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UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE:	
FOSAMAX PRODUCTS LIABILITY LITIGATION	MASTER FILE
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PLAINTIFFS STEERING COMMITTEE'S MEMORANDUM OF LAW IN OPPOSITION TO DEFENDANT'S MOTION TO EXCLUDE EXPERT TESTIMONY ON *DAUBERT* GROUNDS

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ARGUMENT OF THE PLAINTIFFS STEERING COMMITTEE

COMES NOW THE PLAINTIFFS STEERING COMMITTEE ("PSC"), and files this Memorandum of Law in Opposition to Defendant's Motion to Exclude Expert Testimony on *Daubert* Grounds, showing this Court that it should deny the motion for the following reasons.

I. SUMMARY OF ARGUMENT.

Through its *Daubert* challenge to the PSC's experts, Defendant attempts to change the definition of "scientific method" and redefine *Daubert*. In particular, Defendant attempts to persuade this Court that the "scientific method" requires 95% statistical certainty of a causal relationship as determined by a case-controlled epidemiological study. Without it, Defendant asserts, plaintiffs' experts are precluded from relying on Bradford Hill and well established criteria to reach a causal inference based on the totality of the evidence. The scientific process does not operate in this regard, and this fact is reflected in *Daubert* and its progeny. Defendant cannot point to a single published decision in the Second Circuit to support the notion that an expert's opinion is invalid unless it is based on absolute certainty.

To the contrary, courts regularly find expert opinion to be reliable when it is based on the totality of multiple lines of evidence. In this case, the PSC's experts have based their opinions on the well-known basic pharmacology of Fosamax, its similarity in side effects to other bisphosphonates, the published case reports and case series of ONJ, the animal studies, the clinical studies in humans, the analysis of adverse reaction reports by FDA, and other epidemiological data, and the consensus found in textbooks and other learned sources. Under *Daubert* and Rule 702, this Court can readily determine that the evidence is sufficiently reliable basis for the experts' opinions

under generally accepted scientific methods.[1]

II. *DAUBERT* PROVIDES A FLEXIBLE STANDARD OF ADMISSIBILITY AND RECOGNIZES THE EXPANSIVE NATURE OF THE SCIENTIFIC PROCESS.

A. The Scientific Process Results in Etiological Judgments Based upon Observational and Experimental Deductions.

Defendant asserts that causation can only be established under *Daubert* through large controlled epidemiology studies with odds ratios greater than 2.0, a 95% confidence interval, and statistical significance where the "p value" is .05 or less. Defendant further contends that plaintiffs' experts are not entitled to base their opinions on non-epidemiological lines of evidence, including the large volume of published medical literature on Fosamax and the other bisphosphonates. In addition, Defendant suggests that each piece of evidence must stand on its own in order to meet *Daubert's* requirements for admissibility, and that it is impermissible for experts to consider the totality of different lines of converging evidence. In essence, Defendant would have this Court place no value on the totality of the scientific evidence presented which is contrary not only to *Daubert* and subsequent case law but also to the scientific method itself.

"All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time."[2] As leading epidemiologists point out, "By its nature, scientific evidence is cumulative: the more supporting, albeit inconclusive evidence available, the more likely the

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[1] As the reliability of the general causation opinions are established, *infra*, and as Defendant has presented its challenge on the duration of use issue in a separate Motion for Summary Judgment, the PSC will present its arguments pertaining to the three-year issue in its memorandum of law in opposition to the summary judgment motion and incorporates it by reference herein.

[2] Hill, Austin B., *The Environment and Disease: Association or Causation?*, in Section of Occupational Medicine, Jan. 14, 1965, pp. 289-99 (Exh. 2.1000.)

accuracy of the conclusion."[3] Causation in science is an inference, a judgment based upon observational and experimental deductions as well as an understanding of the general laws of nature. Scientists recognize that "causation" should not be regarded as an experimental or epidemiological result, but rather a "judgment" made about the experimental or epidemiological data. *See* ANNOTED REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, SECOND (2004) (hereinafter "REFERENCE MANUAL") p. 517. (Exh. 8.0001).

A single study in isolation is generally not sufficient for a causal inference. In fact, it is scientifically inappropriate not to consider the cumulative effect of all scientific evidence, even when none of evidence on its own is "statistically significant." Science demands that inferences be drawn from the totality of the available science to be able to decide whether the cumulative effect of all the science, rather than the effect of any single piece of it, represents a logical basis for the conclusions.

It is generally recognized by the scientific community that the totality of evidence in this case would include not only epidemiologic data, but also the pharmacological effects of Fosamax, its effects on animals, and the effects of other bisphosphonates on humans and animals.[4] It is simply good science to consider all available scientific evidence when assessing a causal inference. "[B]y focusing on inappropriate criteria applied to determine conclusions, if any, can be reached from any one study, the trial court forecloses testimony about *inferences that can be drawn from the*

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[3] Kenneth Rothman, Noel Weiss, James Robins, Raymond Neutra and Steven Stellman, Interest of Amicus Curiae, Submitted to the Supreme Court, *Daubert v. Merrell Dow,* No. 92-102, 1992 U.S. Briefs 102, at 6 (Dec. 2, 1992 (Exh. 8.0002).

[4] *See* Exh. 2.1000 at pp. 298-99 ("such laboratory evidence can enormously strengthen the hypothesis and indeed, may determine the actual causative agent, the lack of such evidence cannot nullify the epidemiologic observations in man").

combination of results reported by many such studies, even when those studies, standing alone, might not justify such inference." (Ex. 8.0002), Rothman *supra,* (Emphasis added).

Scientists and physicians infer general causation as described above. The scientists and physicians designated as plaintiffs' experts have followed the same appropriate methodology to reasonably infer that Fosamax causes osteonecrosis of the jaw ("ONJ"), from the totality of several lines of evidence that, together, form the body of existing scientific data. This should not be surprising, because several of plaintiffs' experts came to their conclusions prior to this litigation, necessarily following the strictures of real world science. The analyses by the PSC's experts satisfy not only established scientific principles, but also the legal principles underlying *Daubert*.

B. The *Daubert* Standard Is a Flexible One Favoring Admissibility of Expert Testimony.

The Federal Rules of Evidence adopt a general approach of relaxing the traditional barriers to opinion testimony and embody a governing principle favoring admissibility. *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 587-588 (1993) (citing Fed. R. Evid. 401, 402 and 702). Expert testimony is admissible under Rule 702 if: (1) the reasoning or methodology underlying the testimony is scientifically valid (the "reliability" prong); and (2) the reasoning or methodology can properly be applied to the facts in issue (the "relevancy" prong). *Daubert*, 509 U.S. at 592-593; *Campbell v. Metro. Prop. & Cas. Ins. Co.*, 239 F.3d 179, 184 (2d Cir. 2001). As the Court emphasized, the *Daubert* standard is a flexible one and pertinent evidence based on scientifically valid principles will satisfy those demands. *Id.* at 594, 597.

The *Daubert* Court listed four non-exclusive factors to consider in determining whether scientific evidence is reliable: (1) whether the scientific theory or technique can be (and has been)

tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether a particular technique has a known potential rate of error; and (4) whether the theory or technique is accepted in the relevant scientific community. *Id.* at 593-594; *see also Zuchowicz v. United States*, 140 F.3d 381, 386 (2nd Cir. 1998). Research which has been published in a reputable scientific journal after being subjected to the usual rigors of peer review is a significant indication that it is taken seriously by other scientists, i.e., that it meets at least the minimal criteria of good science. *Daubert,* 509 U.S. at 593.

Since *Daubert*, courts have identified additional factors for admissibility. For example, a "very significant factor to be considered is whether the experts are proposing to testify about matters growing naturally and directly out of research they have concluded independent of the litigation, or whether they have developed their opinions expressly for the purposes of testifying." *Daubert v. Merrell Dow Pharm., Inc.,* 43 F.3d 1311, 1317-1318 (9th Cir. 1995) ("*Daubert II*""); *see also Perkins v. Origin Medsystems, Inc.*, 299 F. Supp.2d 45, 58 (D. Conn. 2004); *Awad v. Merck & Co.,* 99 F. Supp.2d 301, 304 (S.D.N.Y 1999) (Stanton, J.); *In re Paoli Railroad Yard PCB Litigation*, 35 F.3d 717, 742 n. 8 (3d Cir. 1994) (stating that an additional factor is the nonjudicial uses to which the method has been put). Such a showing is sufficient if the experts explain "how they went about reaching their conclusions and point to some objective source – a learned treatise, the policy statement of a professional association, a published article in a reputable scientific journal or the like – to show that they have followed the scientific method, as practiced by (at least) a recognized minority of scientists in their field." *Daubert II*, 43 F.3d at 1318-1319.

As will be discussed more fully at § III.D.i.a, *infra*, it is noteworthy that plaintiffs' general causations experts studied and presented dozens of papers on bisphosphonates such as Fosamax

independent of litigation, which adds to the reliability of their opinions. These papers were subjected to peer-review and were accepted for publication in medical and oral surgery journals. In contrast, other than one op.ed. piece by Dr. John Bilezikian, none of Defendant's general causation experts have written and had accepted for publication anything on the topic of bisphosphonates and ONJ.

Scientific evidence is reliable if it is based on an assertion that is grounded in methods of science. *Daubert,* 509 U.S. at 590. The focus is on principles and methodology, not conclusions. *Id.* at 596. It is unreasonable to require the subject of scientific testimony to be "known" to a certainty, since science is an evolving process, and there are no certainties in science. *Id.* at 590. The Supreme Court has recognized that there is a range in which experts might reasonably differ on issues of science, and that such conflicting evidence should be admitted to aid the jury in deciding those issues. *See Kumho Tire Co. v. Carmichael,* 526 U.S. 137, 153 (1999); *Ambrosini v. Labarraque,* 101 F.3d 129, 138-139 (D.C. Cir. 1996) ("there is nothing in *Daubert* to suggest that judges become scientific experts, much less evaluators of the persuasiveness of an expert's conclusion"); *Globetti v. Sandoz Pharm. Corp.*, 111 F. Supp. 2d 1174, 1176 (N.D. Ala. 2000) (role of fact finder, not judge, is to decide whether opinion is correct or worthy of credence). As the Ninth Circuit explained in *Kennedy v. Collagen Corp.,* 161 F.3d 1226, 1230-31 (9th Cir. 1998):

> Judges in jury trials should not exclude expert testimony simply because they disagree with the conclusions of the expert. The *Daubert* duty is to judge the reasoning used in forming an expert conclusion. The test is whether or not the reasoning is scientific and will assist the jury. If it satisfied these two requirements, then it is a matter for the finder of fact to decide what weight to accord the expert's testimony. In arriving at a conclusion, the factfinder may be confronted with opposing experts, additional tests, experiments, and publications, all of which may increase or lessen the value of the expert's testimony. But their presence should not preclude the admission of the expert's testimony – they go to the weight, not the admissibility.

Id.; see also In re Phenylpropanolamine (PPA) Prods. Liability Litigation, 289 F. Supp. 2d 1230, 1249 (W.D. Wash. 2003).

The Second Circuit agrees. *McCullock v. H.B. Fuller Co.*, 61 F.3d 1038, 1044 (2d Cir. 1995). The Court in *McCullock* held plaintiff's expert's testimony was admissible under *Daubert* because it was based on a range of factors, including pathological studies, differential diagnosis, and published medical treatises. The Court emphasized that "[d]isputes as to the strengths of his credentials, faults in his use of differential etiology as a methodology, or lack of textual authority for his opinion, go to the weight, not the admissibility, of his testimony. *Id.* Moreover, a minor flaw in the expert's reasoning or otherwise reliable methodology does not render the expert's opinion inadmissible. *Amorgianos v. Nat'l R.R. Passenger Corp.*, 303 F.3d 256, 267 (2nd Cir. 2002); *Perkins v. Origin Medsystems, Inc.*, 299 F. Supp. 2d 45, 54 (D. Conn. 2004); *McElroy v. Albany Mem. Hosp.*, 332 F. Supp. 2d 502, 505 (N.D.N.Y. 2004) (holding a court should not exclude expert's testimony unless the flaw in the expert's reasoning is large enough that the expert lacks "good grounds" for his conclusion).

As the Second Circuit observed in *Borawick v. Shay*, 68 F.3d 597, 610 (2nd Cir. 1995) (cit.omit):

> [O]ur decision today is informed by the principles underlying the Supreme Court's holding [in *Daubert*]. First, by loosening the strictures on scientific evidence set by *Frye, Daubert* reinforces the idea that there should be a presumption of admissibility of evidence. Second, it emphasizes the need for flexibility in assessing whether evidence is admissible. Rather than using rigid "safeguards" for determining whether testimony should be admitted, the Court's approach is to permit the trial judge to weigh the various considerations pertinent to the issue in question. Third, *Daubert* allows for the admissibility of scientific evidence, even if not generally accepted in the relevant scientific community, provided its reliability has independent support. Finally, the Court expressed its faith in the power of the adversary system to test

"shaky but admissible" evidence and advanced a bias in favor of admitting evidence short of that solidly and indisputably proven to be reliable.

Ultimately, the issue under *Daubert* is whether the methodology employed by the expert constitutes junk science. "The flexible *Daubert* test does not require the judge to step into a white lab coat and perform a rigorous scientific analysis of the proposed expert testimony, but rather 'gives the district court the discretion needed to ensure that the courtroom door remains closed to junk science while admitting reliable expert testimony that will assist the trier of fact.'" *Adesina v. Aladan Corp.*, 438 F.Supp.2d 329, 342 (S.D.N.Y. 2006) (Keenan, J.) (quoting *Amorgianos,* 303 F.3d at 267). As this Court will see below, there is little difference in the methodologies employed by the parties' respective general causation experts - - they simply come to different conclusions. *Daubert* exists solely for the Court to make sure that the methodology employed by an expert is sound, regardless of the expert's conclusions.

III. THE GENERAL CAUSATION OPINIONS PROFFERED BY THE PSC'S EXPERTS ARE VALID AND ARE NOT BASED UPON JUNK SCIENCE.

Applying the flexible *Daubert* standard, this Court should hold that the PSC's general causation experts, Robert Marx, D.D.S., Alastair Goss, B.D.S., D.D.Sc., John Hellstein, D.D.S., M.S., and Mahyar Etminan, Ph.D., M.Sc., are well qualified and employ sufficiently reliable methodology to opine that Fosamax can cause osteonecrosis of the jaws in humans. As referenced in their experts reports at Exhs. 6.0001 (Dr. Etminan), 6.0003 (Dr. Goss), 6.0005 (Dr. Hellstein), and 6.0006 (Dr. Marx), the methodologies utilized by the experts employ the analysis of several lines of scientific evidence, including biologic plausibility, observational studies, prevalence and frequency studies, controlled laboratories studies, and animal studies, which are consistent with the experts' individual opinions that Fosamax causes osteonecrosis of the jaws. Contrary to Defendant's

approach, these experts have engaged in the scientific process by looking at the totality of the evidence. Defendant's argument that each element of the scientific evidence must be capable of proving causation in isolation, without regard to the other lines of evidence, contrary both to the case law and the nature of the scientific process itself.

A. Experts Are Entitled to Reach General Causation Opinions in the Absence of Evidence from Randomized Controlled Trials or Case-control Studies.

Well established case law within the *Daubert* progeny hold that an expert is not required to rely upon evidence from randomized controlled trials or case-control studies in order to reach an opinion on general causation. This is particularly true in the Fosamax case. As Defendant's own epidemiology expert, Dr. Jane Cauley, has testified, randomized clinical trials are not the gold standard for detecting adverse events and accordingly she agrees with the PSC's experts, Dr. Mahyar Etminan and Dr. Curt Furberg. Furthermore, Merck has apparently lost adverse event data on approximately 8,000 of the 25,000 patients from the Fosamax clinical trials program. Merck's own scientists further recognize that the clinical trials program may not have been sensitive enough to pick up data relating to osteonecrosis of the jaw and thus, "the absence of reports does not equal the absence of events". This Court should therefore reject the argument that evidence from these types of studies are required before an expert may express a general causation opinion.

i. *Daubert* Does Not Require a General Causation Expert to Rely upon Case-control or Randomized Control Trial Evidence.

Defendant attempts to preclude every single one of Plaintiffs' generic experts because they do not base their opinions exclusively on epidemiological study evidence. Defendant insists that nothing short of at least one large statistically significant epidemiology study concluding Fosamax causes the injuries alleged can ever pass muster under *Daubert*. Furthermore, Defendant implies that

the failure of Plaintiffs' experts to conduct or rely upon case/control studies specifically to determine whether Fosamax can cause the injuries alleged renders their opinions inadmissible. Defendant also contends that each piece of evidence in isolation must definitively establish causation in order to meet *Daubert's* standard for admissibility. If it were up to Defendant, very few, if any, experts would ever be able to testify before a jury because their opinions would be universally excluded for failure to meet a standard of absolute certainty. This rigid view of admissibility of scientific evidence runs afoul of *Daubert's* intent, as well as an impressive body of of post-*Daubert* case law.

It is particularly unfounded for Defendant to insist that the bases for plaintiffs' experts' opinions are unscientific because they cannot point to any large-scale case/control studies that can demonstrate with "statistical significance" because Defendant was in the best position to conduct large-scale epidemiological studies toexplore the ONJ issue relative to Fosamax, and it chose not to do so. Defendant should not be permitted to use a lack of direct "statistically significant" epidemiological evidence that Fosamax causes ONJ in humans to attack the PSCs' experts, when it is neither feasible nor ethical to conduct the types of studies it claims are required for causation.

a. Courts Applying *Daubert* Have Consistently Rejected the Proposed Requirement That Expert Testimony Rely upon Randomized Controlled Studies .

Contrary to Defendant's viewpoint, there is no mandate under *Daubert* that placebo-controlled studies are a preliminary requirement for expert opinion admissibility. Courts have routinely held that reliance upon non-epidemiological study evidence is admissible to prove causation. *See, e.g., Kennedy*, 161 F.3d at 1229 (finding expert testimony was admissible based on reliable methodology without epidemiological or animal studies to link defendant's product to plaintiff's disease); *Ambrosini*, 101 F.3d 129, 135-138 (finding expert's testimony was admissible

where it was based on multiple sources of non-epidemiological study evidence, including published medical literature, biological plausibility and time sequence); *Benedi v. McNeil-P.P.C., Inc.*, 66 F.3d 1378, 1384 (4th Cir. 1995) (holding experts properly relied on non-epidemiological study data to support their conclusions); *Glaser v. Thompson Med. Co.*, 32 F.3d 969, 972 (6th Cir. 1994) (finding expert's opinion was admissible where it was based on his own published studies, articles in other published peer-reviewed journals, published case reports and his own clinical experience).

The Second Circuit has also deemed experts' opinions on causation admissible based on non-epidemiological evidence. *See, e.g., Zuchowicz*, 140 F.3d at 381-383 (2nd Cir. 1998) (finding expert's testimony was admissible based on differential diagnosis, along with a variety of published and unpublished studies indicating that drug's affect on hormones could cause endothelial dysfunction and an imbalance of vasoconstrictor effects, resulting in primary pulmonary hypertension); *McCullock,* 61 F.3d at 1044; *see also Becker v. National Health Prods., Inc.*, 896 F. Supp. 100, 103 (N.D.N.Y. 1995) (holding experts' opinions were reliable where they based their opinions on a variety of factors, including medical history, scientific and medical treatises and articles, and their training and experience); *McElroy*, 332 F. Supp. 2d at 506 (finding lack of specific textual authority for expert's opinion did not render it inadmissible).

In *Zuchowicz,* the court admitted the testimony of well-qualified experts who had neither direct epidemiological nor anecdotal evidence to rely upon to show that the unintentional overdose of Danocrine plaintiff ingested caused her to develop the rare disease primary pulmonary hypertension: nevertheless, their opinions were deemed reliable based on the well-reasoned application of biological plausibility and differential diagnosis. 140 F.3d at 385-386. Similarly, the court in *McCullock* held that the plaintiff's expert's testimony was reliable because he based his

opinion on a variety of non-epidemiological factors, such as medical textbooks and differential diagnosis. The court explained, "Disputes as to the strength of his credentials, faults in his use of differential etiology as a methodology, or lack of textual authority for his opinion, go to the weight, not the admissibility, of his testimony." *McCullock*, 61 F.3d at 1044 (citing *Daubert*).

The Second Circuit's flexible consideration of the admissibility of expert testimony is entirely consistent with other jurisdictions. For example, the *Ambrosini* court noted, "Even where a party has admitted that no biochemical or epidemiological test has been done that can conclusively establish a link between a drug and an illness, their expert evidence on the subject is not rendered inadmissible." *Ambrosini*, 101 F.3d at 138. The court also emphasized that it is improper to conflate the issues of admissibility of expert testimony and the weight to be accorded to it by attempting to evaluate the credibility of opposing experts and the persuasiveness of competing scientific studies, which must be decided by the factfinder. *Id.* at 141.

The Fourth Circuit Court in *Benedi* explained:

> [W]e do not read *Daubert* as restricting expert testimony to opinions that are based solely upon epidemiological data. *Daubert* merely requires that the expert testimon be relevant and reliable ... Under the *Daubert* standard, epidemiological studies are not necessarily required to prove causation, as long as the methodology employed by the expert in reaching his or her conclusion is sound.

Benedi, 66 F.3d at 1384.

The Benedi court found that plaintiff's experts relied on a multiple of factors, including a study of the peer-reviewed literature and concluded, "We will not declare such methodologies invalid and unreliable in light of the medical community's daily use of the same methodologies in diagnosing patients." *Id.*

In *Globetti*, the court made the following observations regarding the admissibility of evidence

in situations where no epidemiological studies had been – or feasibly could have been – conducted:

> While an epidemiological study may be the best evidence, Daubert requires only that reliable evidence be presented, and that evidence here consists of the animal studies, the medical literature reviews, the ADRs reported to the FDA, the 'general acceptance' of the association in several medical tests [and other data]. These all are recognized and accepted scientific methodologies, used for assessing the possible side-effects and hazards associated with particular drugs and the causes of disease. The fact that Mrs. Globetti's AMI was caused by her ingestion of Parlodel can be reliably inferred from the facts known about the vaso-constrictive effect of bromocriptine.

Id. at 1179. The court also pointed out, "Science, like many other human endeavors, draws conclusions from circumstantial evidence when other, better forms of evidence is not available." *Id.* at 1180. Indeed, courts in the Second Circuit and other jurisdictions routinely admit expert testimony based not on epidemiology but upon differential diagnosis. *See Zuchowicz,* 140 F.3d at 390; *McCullock*, 61 F.3d at 1044; *Perkins*, 299 F. Supp. 2d at 56-57; *In re Paoli,* 35 F.3d at 758 (differential diagnosis is "a technique that has widespread acceptance in the medical community, has been subject to peer review, and does not frequently lead to incorrect results").

Here, Defendant's rejection of the impressive body of evidence showing a causal relationship between Fosamax and ONJ, both epidemiological and non-epidemiological, is misguided. Defendant also erroneously attempts to conflate the issues of admissibility and credibility of expert testimony. Disputes as to the significance of the data are questions of fact for the jury to consider. *See, e.g., Derienzo v. Trek Bicycle Corp.*, 376 F.Supp.2d 537, 569 (S.D.N.Y. 2005) (McMahon, J.) (holding that such "forensic quibbles" go to the weight of the evidence and not admissibility and are thus within the province of the jury).

b. Expert Causation Testimony Regarding Other Drugs Based on Nearly Identical Lines Evidence Has Been Held Admissible under *Daubert*.

As discussed above, the Sixth Circuit upheld the admissibility of expert testimony that phenylpropanolamine (PPA) could cause stroke, based on published studies, case reports and data strikingly similar to the non-epidemiological evidence presented here. *Glaser*, 32 F.3d at 972. In addition, Judge Barbara Rothstein's *Daubert* opinion regarding the admissibility of expert testimony in the PPA multi-district litigation is particularly instructive. The type of evidence plaintiffs' generic experts presented to the court in the PPA MDL was similar to the data relied upon by Plaintiffs' experts in this litigation. Their opinions were based upon multiple lines of evidence, including: 1) biological plausibility in light of the well known pharmacology of PPA; 2) analogy to closely related drugs in the same pharmacological class; 3) published peer-reviewed case reports; 4) human clinical studies on blood pressure; 5) animal studies; 6) FDA's adverse event reports; and – in the case of hemorrhagic stroke – 7) the findings of a case/control epidemiology study. *In re Phenylpropanolamine (PPA) Litig.*, 289 F. Supp. 2d at 1234-1235.

As here, the defendants in the PPA litigation moved to exclude the testimony of every plaintiffs' generic expert, claiming: 1) that the Hemorrhagic Stroke Project was unreliable because it contained numerous flaws; and 2) the experts relied upon supposedly invalid and non-scientific evidence to support their opinions that PPA could cause hemorrhagic stroke, including case reports, textbooks and treatises, adverse drug reports, animal studies and analogies to similar drugs. The PPA defendants made many of the same arguments Merck makes here. *Id.* at 1242. However, the court rejected the PPA defendants' claims, "Defendants isolate these sources, rather than considering *the whole*. Non-epidemiological sources are frequently utilized by experts in rendering scientific opinions and, under *Daubert*, should be considered by the court in assessing the reliability of those opinions." *Id.* (citations omitted) (emphasis added).

The court in the PPA MDL also held that expert testimony offered by Dr. Steven R. Levine was admissible on the question of whether PPA could cause ischemic stroke, for which there was no epidemiologic study evidence. *Id.* at 1246-1247. Dr. Levine's opinion was based on "case and adverse drug event reports, biological plausibility, comparison to other sympathomimetics and naturally occurring conditions with altered sympathetic tone, PPA blood pressure studies, textbook and other references, and both his own and others' clinical experience." *Id.* at 1246. There was no case-control study evidence supporting his testimony, but the court noted that the lack of epidemiology evidence did not invalidate his opinions. *Id.* To the contrary, Dr. Levine, like the other plaintiffs' experts, employed good science in reaching his conclusions. Accordingly, the experts' reliance on other non-epidemiological evidence tying PPA to ischemic stroke was admissible:

> In addition to the evidence proffered as to biological plausibility and through comparison to like agents, plaintiffs' experts rely on case and adverse drug reports, textbooks and treatises, and the clinical experience of several experts and other scientists. The court again finds that the cumulative effect of this evidence satisfies the mandate of *Daubert*.

Id. at 1248.

The evidence presented by Plaintiffs' experts in the Fosamax litigation is similar to – and in many ways stronger – than that offered by the experts in the PPA litigation. Here, Defendant moves to exclude each of Plaintiffs' generic experts from testifying for the same reasons the defendants did in the PPA case. As set forth below, the cases Defendant cites in support of its contention that epidemiology is required to prove general causation are readily distinguished. Neither *Daubert* nor the Rules of Evidence ever intended such a rigid and unrealistic result. As the D.C. Circuit Court in *Ferebee v. Chevron Chem. Co.*, 736 F.2d. 1529 (D.C. Cir. 1984) noted:

> [A] cause-effect relationship need not be clearly established by animal or epidemiological studies before a doctor can testify that, in his opinion, such a relationship exists. As long as the basic methodology employed to reach such a conclusion is sound, such as use of tissue samples, standard tests, and patient examination, products liability law does not preclude recovery until a "statistically significant" number of people have been injured or until science has had the time and resources to complete sophisticated laboratory studies of the chemical. In a courtroom, the test for allowing a plaintiff to recover in a tort suit of this type is not scientific certainty but legal sufficiency ...

Id. at 1535-36; *see also Wells v. Ortho Pharm. Corp.*, 788 F.2d 741, 745 (11th Cir. 1986) (same).

Both legal and scientific scholars have criticized the insistence by some courts upon epidemiological proof in order to establish general causation. For example, Joe Cecil, Ph.D., J.D. of the Federal Judicial Center and Dr. Jerome Kassirer of Tufts University analyzed how some federal courts treat the admissibility of experts' opinions on general causation. Publishing in the Journal of the American Medical Association, the authors wrote that by imposing a standard that is inconsistent with medical practice, some courts exclude from the jury's consideration the opinions of expert clinicians based on the judgments they make daily regarding causation.[5]

In Fosamax, the PSC's experts rely on multiple lines of scientific evidence, all pointing in the same causal direction: Fosamax can cause the injuries alleged. The combination and totality of data upon which the experts rely are of the same type that several courts have held to be admissible. The evidence includes: including biologic plausibility observational studies, prevalence and frequency studies, controlled laboratories studies, and animal studies, which are consistent with the experts' individual opinions that Fosamax causes osteonecrosis of the jaws. For most of the PSC's experts, actual clinical experience with ONJ caused by bisphosphonates informed their

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[5] Kassirer, J.P. & Cecil, J.S., *Inconsistency in Evidentiary Standards for Medical Testimony – Disorder in the Courts,* 288(11) JAMA 1382-1387 (2002) (Exh. 2.1001).

overall opinions. More important, physicians routinely rely upon this type of evidence in diagnosing and treating patients. Reliance upon consistent, converging sources of evidence is a generally accepted methodology for assessing cause and effect.

Therefore, it is clear under *Daubert* and its progeny that the evidence presented by plaintiffs' experts is sufficiently grounded in good science to be admissible without additional epidemiological studies.[6] Defendant failed to conduct the studies it now claims are essential to establish definitive causation and that should not be grounds for excluding the PSC's experts' testimony.

ii. Randomized Controlled Trials Are Not the Gold Standard for Detecting Rare Adverse Events Such as Osteonecrosis of the Jaws.

Beginning at page 14 of its *Daubert* brief, Defendant presents as an *a priori* assumption the notion that Randomized Controlled Trials ("RCTs") are the gold standard for detecting adverse events in relationship to the use of a drug. This argument, however, fails to recognize the huge exception to such a sweeping statements: RCTs are usually insufficiently powered to detect adverse events which occur rarely. Also, this argument also reflects Merck's myopic view of what constitutes causation. The following example from Merck's Vice President of Epidemiology is remarkably illustrative in how Merck views causation evidence: "And, you know, with anything, even with lung cancer. We can't do a randomized clinical trial on cigarette smoking. So I can't show cause and effect. But I'm pretty sure that cigarette smoking and cancer are related." (Exh.

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[6] Even the Parlodel line of cases that defendants cite reject the proposition that epidemiological evidence is required for an expert's opinion to be valid. *See Glastetter v Novartis Pharm. Corp.*, 252 F.3d 986, 992 (8th Cir. 2001) ("a plaintiff need not introduce epidemiological evidence of causation in order to satisfy *Daubert's* threshold for admission of expert medical testimony); *Hollander v. Sandoz Pharm. Corp.*, 289 F.3d 1193, 1211-1212 (case reports and differential diagnosis may be admissible in other litigations) (10th Cir. 2002); *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1199 ("This court has long held that epidemiology is not required to prove causation in a toxic tort case." (11th Cir. 2002). It should also be noted that the evidence in the Parlodel cases was far weaker than the substantial amount of evidence on Fosamax and its known capacity to cause osteonecrosis of the jaws.

3.0009: 203:19-204:1.)

The PSC's expert Dr. Mahyar Etminan, a pharmacoepidemiologist whose credentials are discussed at § III.B.i, has identified this fallacy and even Defendant's expert epidemiologist, Dr. Jane Cauley, agrees that RCTs are not the gold standard for detecting adverse events in a population. Merck's own employees have expressly recognized that Merck's clinical trials likely would not have detected incidences of osteonecrosis of the jaw, had they occurred. Furthermore, Merck cannot locate adverse event data on one-third of its Fosamax clinical trial patients and therefore cannot be heard to claim that it detected no cases of osteonecrosis of the jaw throughout its clinical trials.

a. Dr. Etminan, Dr. Furberg, and Dr. Cauley Agree That RCTs Are Not the Gold Standard for Detecting Adverse Events.

In his expert report, Dr. Etminan explains that RCTs are among the evidence that epidemiologists can rely upon; however, because of their inherent limitations, RCTs can be inferior to other lines of scientific evidence: "Although RCTs are considered the optimal study design to establish drug efficacy, they may be inferior to observational studies in quantifying rare adverse events mainly due to lack of sample size and at times ethical issues. In such circumstances causality must be established from other types of evidence including case-reports, case-series and observational studies." (Exh. 6.0001: p. 4.)

PSC clinical trial and drug safety expert Dr. Curt Furberg agrees. Dr. Furberg is a past charter member of the U.S. Food & Drug Administration Drug Safety and Risk Management Advisory Committee, which was established by the FDA to provide expert advice on drug safety issues. (Exh. 6.0002: p.4.) Even though Dr. Furberg's term ended in May 2006, the FDA invited him to serve as an expert at two FDA hearings convened in the Fall of 2008. (Exh. 6.0002: p.4.)

As an invited expert witness, he has also testified on multiple occasions at Congressional hearings relating to drug safety. (Exh. 6.0002: p.4.) Dr. Furberg has authored numerous publication on the subject of clinical trials including co-authoring the treatise *Fundamentals of Clinical Trials*, 3rd ed. (Exh. 6.0002: pp.5-6.) Dr. Furberg explains the generally accepted limitations of using RCTs for detecting adverse events:

> The number of patients required for pre-approval studies is inadequate for detecting adverse events occurring at a rate of one in 1,000 person-years. Second, adverse events that only occur after an extended exposure to a drug are typically missed since the pre-approval trials are typically not long enough to detect late-occurring adverse events. Third, unexpected adverse events are difficult to detect since they are not looked for.

(Exh. 6.0002: p.28.)

Defendant's epidemiology expert, Dr. Jane Cauley agrees, albeit for different reasons. Dr. Cauley was one of the principal investigators for Merck's largest Fosamax clinical trial, the Fracture Intervention Trial ("FIT"). (Exh. 4.0002: 11:2-12:22.) [redacted]

[redacted]

counsel asked Dr. Cauley the following questions to which she responded:

Q: All right. And is it your testimony that clinical trials are the gold standard for determining whether there is an association between an adverse event and a pharmaceutical agent?

A: No, I - - I would not agree with that.

Q: Okay. Why don't you agree with that?

A: Because the problem with the clinical trial data is that we look at many adverse events, and just by chance alone, some of them may be significant by chance. So I think that an adverse event needs to be biologically plausible. There has to be other data besides just a chance P value less than .05.

Q: Right. And that's why observational data and the concept of assessing the risk between a drug and an adverse event can be very, very important in that analysis, right?

A: Yes.

(Exh. 4.0002: 29:10-30:2.)

b. Merck's clinical trials were not designed to detect adverse events relating to osteonecrosis of the jaws.

Beginning at page 14 of its *Daubert* brief, Defendant argues that there is no evidence from the Fosamax RCTs that Fosamax is associated with an increased risk of ONJ. Defendant fails to mention, however, that the studies were not powered to detect, nor designed to elicit, adverse events relating to osteonecrosis of the jaw.

In all of the discovery conducted so far, the only clinical trial that has been identified as

having any oral surgery monitoring component was the 1999-2000 periodontal study which Merck conducted on 335 subjects and controls for a two year period. (Exh. 3.0003: 172:1-174:17, Exh. 3.0005: 26:15-29:3.) Citing the incidence estimates from the FDA-funded PROBE study of approximately 1 osteonecrosis of the jaw case per 1,100 users, Dr. Etminan explains that with a treatment arm of less than 200 patients, one would not expect to find any cases of osteonecrosis of the jaw, even if the study was designed to look for such cases. (Exh. 6.0001: pp. 5-6.)

The PSC took the deposition of Dr. Michael Goldberg, the former director of Merck's Clinical Risk Management and Safety Surveillance department. (Exh. 3.0005: 175:10-175:15.) As the Merck employee responsible for Fosamax safety surveillance, Dr. Goldberg participated in the drafting of Merck's statement that it had no reports of osteonecrosis of the jaws in any of its 17,000 clinical trial patients. (Exh. 3.0005: 22:7-23:1.) The statement can still be found on Merck's website to this day.[7] (As explained below, however, Merck had 25,000 clinical trial patients - - far more than the "17,000" clinical trial patients it references in its Fosamax/ONJ statement.)

Dr. Goldberg explained that *none* of Merck's clinical trials were designed to detect any information relating to osteonecrosis of the jaws:

> Q: . . . But the specific event of osteonecrosis of the jaw or denuded bone or exposed bone or dead bone in the jaw was not particularly targeted in any of the clinical trials to which we have been discussing today, right?
>
> A: It was not specifically targeted, no.
>
> Q: And the coding issue was the same. There was no [ICD-9] code for osteonecrosis of the jaw at the time the Merck clinical trials were being conducted, correct?
>
> A: Correct, that there was not a specific code for osteonecrosis of the jaw.

[7] http://www.merck.com/newsroom/press_releases/product/fosamax_statement.html (Exh.8.0003.)

Q: And in the overwhelming majority of the 17,000 patients in the Merck clinical trials which is referred to in Merck's public statement, none of them had as investigators or monitors sponsored by the study prescribed and mandated dental examinations for the purpose of seeing whether there is a problem with exposed or dead bone in the jaw, right?

A: That was not a consideration at that point in time in the clinical trials.

(Exh. 3.0005: 50:22-52:2.)

[redacted]

Dr. Donald Kimmel features prominently in Merck's understanding of the ONJ situation. Dr. Kimmel is a dentist who is also a bone scientist. (Exh. 3.0001:189:1-189:6.) He was the only dentist then working at Merck, according to Dr. Santora. (Exh. 3.0010: 234:9-234:15.) His official role was in the department of molecular endocrinology (Exh. 3.0006: 45:12-46:11), and according to the department's manager, Dr. Alfred Reszka, there was no one in that department as knowledgeable about ONJ and Fosamax as Dr. Kimmel. (Exh. 3.0007: 112:6-113:22.) The successor to Dr. Goldberg, Dr. Thomas Bold, explained that Dr. Kimmel was instrumental in Merck's assessment of the osteonecrosis of the jaw sissue with respect to Merck's drug, Fosamax. (Exh. 3.0002: 84:17-84:25.) Accordingly, Merck selected Dr. Kimmel to speak about Fosamax and ONJ to medical associations, on Merck's behalf. (Exh. 3.0001: 190:15-191:4.)

[redacted]

c. Merck has not disclosed with the public the data relating to the other 8,000 Fosamax clinical trial patients.

At page 15 of its brief, and without addressing specifics, Defendant generically refers to the absence of osteonecrosis of the jaw reports in its clinical trials. While Merck has retained and paid Dr. John Bilezikian as an expert, it simply cites his 2006 editorial published in the New England Journal of Medicine for support. As referenced above, Merck's public statement on the topic referred to 17,000 clinical trial patients. [redacted] In any event, Merck epidemiologist Dr. Nancy Santanello has testified that you simply cannot conduct an RCT for purposes of detecting osteonecrosis of the jaws. (Exh. 3.0009: 72:15-73:5.)

Accordingly, because none of Merck's clinical trials were designed to look at the topic of osteonecrosis of the jaw, or sensitive enough to pick up ONJ manifestations, Merck should not be permitted to infer that it studied the osteonecrosis of the jaw issue when it has not - - particularly in

light of the fact that it is apparently unable to locate adverse event data from some 8,000 patients.

iii. According to Merck, the Relationship of Fosamax to Osteonecrosis of the Jaws Cannot Be Assessed Through Any Epidemiologic Study.

a. Merck Deliberately Decided Neither to Conduct Nor Fund Any Epidemiologic Study Relating to Fosamax and ONJ.

Defendant was in the best position to conduct large-scale epidemiological studies to study the relationship of Fosamax and ONJ, and it chose not to do so. Long after Merck received notice of ONJ cases related to Fosamax use, its scientists debated whether to study the relationship epidemiologically. Ultimately, Merck chose not to conduct or fund any such study. It should not be permitted to point to the absence of such a study as ground for excluding the expert evidence presented by the PSC.

[redacted]

To explain why it has not conducted any study, Defendant has taken the position that it is simply impossible to conduct any such study because, until recently, there was no ICD-9 code for osteonecrosis of the jaws.[9] (Exh. 3.0009: 41:20-43:8, 44:3-46:19, 58:9-60:10.) Dr. Santanello further testified, however, that even positive epidemiology studies do not themselves show cause and effect, leading to her comment that you cannot even show cause and effect between cigarette smoking and lung cancer. (Exh. 3.0009: 202:16-204:1.) It is apparent through this testimony that Defendant is attempting to hold scientists to an impossibly high and unrealistic standard of causation. This Court should not sanction such a restrictive requirement as it is counter to the overwhelming consensus of legal decisions under *Daubert* and the Federal Rules of Evidence.

[redacted]

[9] At page 16 of its memorandum, Defendant cites a study by Dr. Athanasios Zavras, using a surrogate code approach, the PSC feels is important for this Court to know that Merck internally rejected Dr. Zavras' approach [redacted]

B. The PSC's General Causation Experts Are Qualified to Appreciate the Causation Significant of and Rely Upon Multiple Lines of Reliable Scientific Evidence Supporting Their Opinions That Fosamax Can Cause Osteonecrosis of the Jaws.

Relying on sound methodologies, the PSC's general causation experts concluded, long before they were ever retained by plaintiffs' counsel, that Fosamax could cause ONJ. Drs. Goss, Hellstein and Marx all published peer-reviewed articles on the causal link between bisphosphonates and ONJ before they were ever contacted by any attorneys for plaintiffs. These experts were the first to recognize and study the link between bisphosphonate use and ONJ, which is why they have been chosen repeatedly to serve on advisory boards and expert panels of the American Dental Association and the American Association of Oral and Maxillofacial Surgeons regarding bisphosphonate-related ONJ. Moreover, Dr. Etminan, a respected pharmacoepidemiologist who serves as an academic reviewer for numerous peer-reviewed journals in the field of pharmacoepidemiology and who himself has conducted a nexted case-control study addressing the relationship between Fosamax and ONJ, has never been involved in any litigation prior to this MDL.

i. The PSC's General Causation Experts Are Eminently Qualified to Offer Their Scientific Opinions Relating to the Ability of Fosamax to Cause Osteonecrosis of the Jaws.

All of the PSCs' experts are highly credentialed experts and are renowned in their respective fields. The experts are superbly qualified to give their opinions that Fosamax can cause the injuries at issue. The oral medicine experts have direct clinical experience studying bisphosphonates, as well as diagnosing and treating patients injured by these drugs. They came to their conclusions that bisphosphonates could cause osteonecrosis of the jaws, and they have published those opinions to their colleagues in peer-reviewed medical journals, long before they were ever contacted by counsel

for the PSC. The experts' qualifications are set forth in their affidavits and curriculum vitae which are attached to this memorandum as exhibits. Upon review of the experts' CV's, this Court will see that between them, the experts have authored more than 30 publications published in well respected medical journals directly addressing the topic of bisphosphonates and osteonecrosis of the jaws. In contrast, among the football team of general causation experts identified by Defendant, none of them have written any article on the topic other thana single opinion editorial authored by Dr. John Bilezikian.[10]

The PSC's experts build the foundations for their opinions on the following scientific evidence: the well-known pharmacology of bisphosphonates, the animal and human clinical studies on the pharmacological effects of Fosamax, the numerous case reports, case series, human study data (including a prevalence study commissioned by the FDA), analysis of adverse event data, the wealth of information in peer-reviewed, published medical literature, and in several instances, the experts' own studies and clinical experience. The experts' reliance on the totality of these converging lines of evidence is generally accepted as proper scientific methodology in assessing the likely causal relationship between a pharmacological agent and a given injury.

a. Dr. Goss: "you absolutely earned the good feedback!"

Dr. Goss is a world-renowned expert in the field of oral and maxillofacial surgery, and in particular, the treatment of osteonecrosis of the jaw. Practicing half-way around the globe from Dr. Marx, Dr. Goss had a clinical experience in his native Australia that was strikingly similar to that

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[10] While Dr. Robert Glickman's name appeared as a co-author of a recent publication in the Journal of Oral & Maxillofacial Surgery, he readily admitted that he did not write the first word in the article, nor did he conduct any of the research contained in the report. Rather, he simply served as an editorial advisor to the lead author; accordingly, he agrees that he has not written anything on the topic of bisphosphonates and osteonecrosis of the jaws that has been published in a peer-reviewed journal. (Exh. 4.0005: 141:24-143:9.).

reported by Dr. Marx. In 2003, Dr. Goss came across a small group of patients exhibiting a unique and previously unseen form of ONJ marked by pain and difficulty healing (Exh. 5.0003: 18:11-19:5). Like Dr. Marx in the United States, Dr. Goss observed that all of the patients presenting with this unique form of ONJ were on bisphosphonates. (Exh. 5.0003: 18:11-18:25.)

Dr. Goss was one of the authors of a peer-reviewed article entitled "Nature and Frequency of Bisphosphonate-Associated Osteonecrosis of the Jaw" published in the *American Association of Oral and Maxillofacial Surgeons* (2007) (Exh. 2.0348). The study revealed a significant incidence of the unique form of ONJ associated with use of bisphosphonates. Patients on weekly oral alendronate (Fosamax) had a frequency of ONJ of 1 in 2,260 to 8,470. Among patients who had undergone an extraction, this frequency increased to 1 in 296 to 1,130. Dr. Goss's study has been well received within the scientific community, including researchers within Merck. Dr. Goss invited Merck to comment on the study and to provide prescription estimate data which would help Dr. Goss arrive at the denominator for his frequency rate conclusions. (Exh. 3.0004: 362:14-365:14, 367:12-369:22.)

Dr. Donald Kimmel is the only dentist who worked on Fosamax for Merck. (Exh. 3.0003: 45:9-46:1.) Dr. Kimmel, a bone physiologist and dentist with responsibility for Merck's osteonecrosis of the jaw assessement, contradicted Merck's now-implicit criticisms of this study. [redacted]

[redacted]

[redacted]

[redacted]

Dr. Anastasia Daifotis is a clinical researcher at Merck who served as the general manager responsible for Merck's Fosamax franchise. (Exh. 3.0003: 14:12-15:14.) In the Summer of 2006, her department organized an invited consultants meeting at which Merck invited experts on the topic of osteonecrosis of the jaws to make presentations to Merck. (Exh. 3.0003: 16:11-17:8.) Merck recognized the expertise of Dr. Goss by inviting him to attend a September 2006 consultants meeting at Merck. (Exh. 3.0003: 50:20-56:10.) [redacted]

[redacted]

Merck's own research scientist's comments belie Merck's assertion that Dr. Goss has not

used accepted methodologies in reaching his opinions regarding the link between Fosamax ingestion and ONJ. Like the other world-renowned experts who have found such a causative link, Dr. Goss has the expertise to recognize the unique form of ONJ observed in bisphosphonate users and has demonstrated the causal link between Fosamax and ONJ using sound scientific methodologies.

Dr. Goss has testified unequivocally that Fosamax causes ONJ. (Exh. 5.0003: 88:8-88:20.) While the trial deposition of Dr. Goss has already been taken by the PSC[11], and is submitted in its entirety, the PSC directs the Court's attention to the salient elements of Dr. Goss' opinions as follows:

- Dr. Goss explains the propensity of Fosamax to have its deleterious effects on the jawbones specifically, rather than all the bone in the body, because the jaws are distinct from the long bones of the body. Among the differences are: the way the bones are originally formed, the type of bone itself, the greater presence of osteoclasts in jawbone, and the proximity of jawbone to a bacteria-rich environment. (Exh. 5.0003: 55:25–59:17.) Importantly, jawbone also "turns over" at a rate ten times faster than long bones. (Exh. 5.0003: 60:2–12.) This turnover is the process by which bone renews itself.

- The bisphosphonate class of drugs, including Fosamax, is designed to suppress osteoclastic activity (bone resorption). (Exh. 5.0003: 95:18–96:5.) In Dr. Goss' research, the CTX value, which is a measure of bone turnover, declines after a patient has been on Fosamax for six weeks—indicating that by inhibiting resorption, Fosamax actually stalls the process of bone turnover, and does so relatively quickly. (Exh. 5.0003: 118:2–119:2; 96:10–97:1.) The shortest amount of time which he has seen ONJ develop in a Fosamax patient is twelve weeks. (Exh. 5.0003: 111:14–112:1.)

b. Dr. Marx: "you are the best one to lead the discussion."

Dr. Marx is a preeminent maxillofacial surgeon, who has authored numerous monographs,

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[11] Contrary to Defendant's assertion in its *Daubert* motion that Dr. Goss has testified regarding undisclosed opinions, Dr. Goss' reliance bases were clearly identified in his report referencing the research materials he authored, including as of yet unpublished materials which were given to Merck's counsel well in advance of the Dr. Goss' deposition,such as the manuscript, "Alveolar Bone & the Bisphosphonates," by A. Cheng, C.G. Daly, B.M. Logan, and A.N. Goss, and which is attached hereto as Exh. 5.0003.

textbooks and peer-review articles on the subject of diagnosis and treatment of maxillofacial diseases and disorders. His textbook on maxillofacial pathology won the American Medical Writers Best Book of the Year Award for 2002. Dr. Marx is a recognized leader in the field of treatment and diagnosis of osteonecrosis of the jaw and physicians, dentists and fellow oral and maxillofacial surgeons routinely refer cases of necrosis of jaw bone to Dr. Marx for diagnosis and treatment. As this Court is aware, Dr. Goss has published a book on the topic: "Oral & Intravenous Bisphosphonate-Induced Osteonecrosis of the Jaws: History, Etiology, Prevention, and Treatment," by Robert E. Marx, DDS.

Beginning in 1999, Dr. Marx encountered a number of unique cases of osteonecrosis of the jaw (ONJ), which unlike the many cases of osteonecrosis he had treated throughout his career, were unresponsive to treatment and were not attributable to known etiologies of ONJ such as infection or exposure to radiation. In all, he has treated 182 patients with this unique, readily identifiable condition. The only common denominator in every single one of these cases was the use of bisphosphonates. Of these cases, 50 involved the oral bisphosphonate, alendronate, otherwise known as Fosamax. In his 25 years of experience as a recognized authority in the treatment of ONJ, other than those patients who were irradiated or had a disease known to cause ONJ, he has *never* seen a case of ONJ in a patient who had not received bisphosphonates. (Exh. 6.0006: ¶¶ 8, 37.)

[redacted]

Dr. Marx's report discloses that he is of the professional opinion that Fosamax causes osteonecrosis of the jaws. The PSC directs the Court's attention to the salient elements of Dr. Marx's opinions as follows:

- Dr. Marx's identifies the likely mechanism of causation as follows: because the jaws have a greater bone turnover rate, bisphosphonates are attracted to them at higher concentrations and have a greater effect on them. (Exh. 6.0006: ¶¶ 34, 29.) Bisphosphonates inhibit and almost completely stop bone turnover, "directly kill[ing] a normal cell in the human body." (Exh. 6.0006: ¶¶ 35, 36.) Micro-injuries, or even the ordinary impact of constant jawbone movement, require the jawbones to remodel at a greater rate than other types of bone. (Exh. 6.0006: ¶¶ 34, 30.) But because the process of turnover is so inhibited, remodeling fails. (Exh. 6.0006: ¶¶ 30-34.)

- His opinion regarding the mechanism of action is supported by his explanation of the CTX test, a test which measures a marker in the blood that shows suppression of bone turnover. As addressed more fully below, bone turnover markers levels decline when Fosamax is present in the body. (Exh. 6.0006: ¶ 39.)

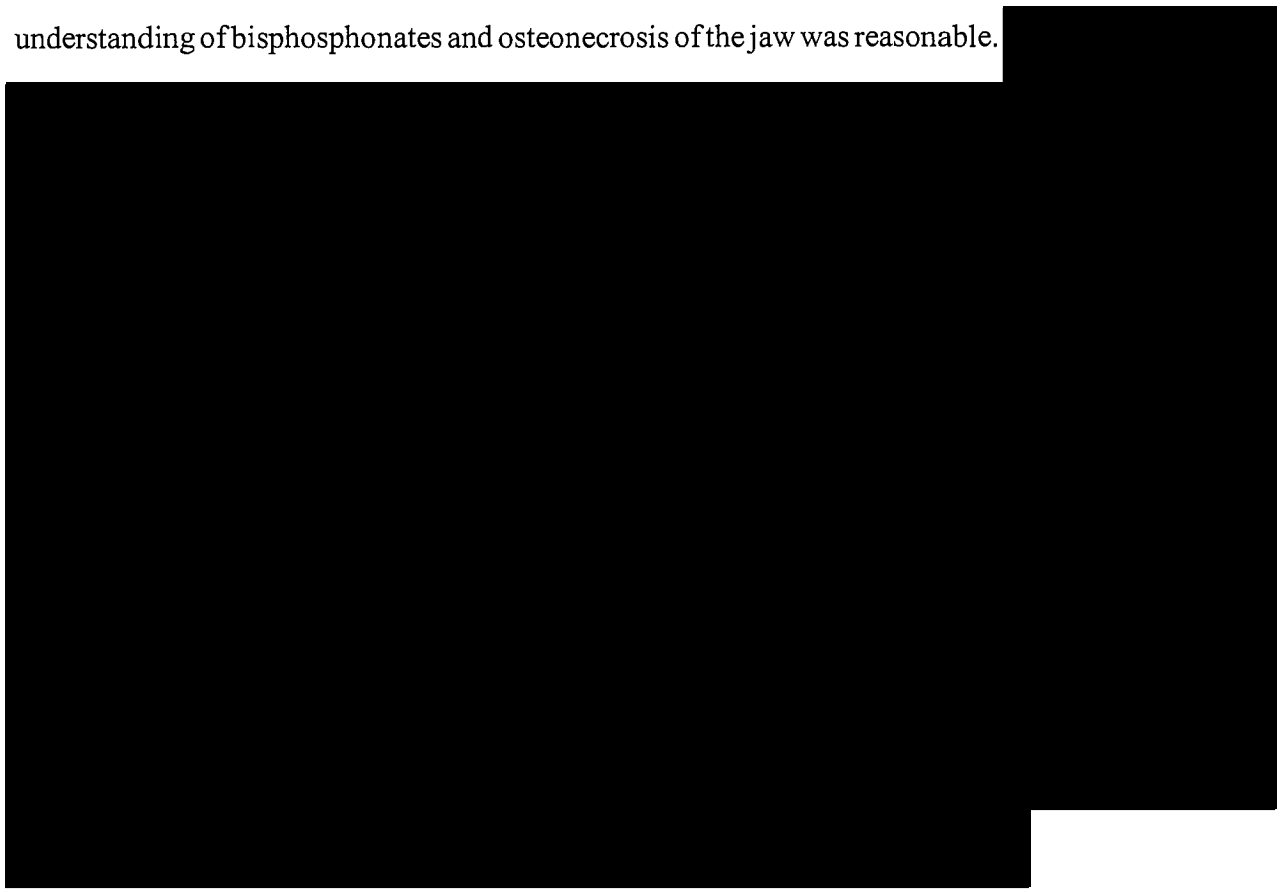
- He has never found a case of ONJ (as defined by the American Association of Oral and Maxillofacial Surgeons), that did not have a history of nitrogen-containing bisphosphonate use. (Exh. 6.0006: ¶¶ 8, 37.)

c. Dr. Hellstein: "he seems pretty reasonable in his approach."

Like Drs. Goss and Marx, Dr. Hellstein is an internationally recognized expert in the diagnosis and treatment of diseases of the jaw. He is board certified by the American Board of Oral

Pathology, and serves on the Expert Panel on Oral Bisphosphonates for the American Dental Association. (Exh. 6.0005, at Hellstein CV, p.3.) Through the well-established methodology of differential diagnosis, Dr. Hellstein has concluded to a reasonable degree of medical certainty that this new disease is caused by bisphosphonate use.

Merck's Director of Clinical Research, Dr. Arthur Santora, acknowledged that Dr. Hellstein's understanding of bisphosphonates and osteonecrosis of the jaw was reasonable.



Dr. John Hellstein is a D.D.S. and a clinical professor at the University of Iowa, College of Dentistry. (Exh. 6.0005, p. 3.) Based on his clinical experience, as well as his review of approximately 250 articles in a medical database, Dr. Hellstein believes that "the problem of BON is real." (Exh. 6.0005, p. 16.) He emphasizes that medical practitioners "DO NOT see BON in patients without a history of bisphosphonate use." (Exh. 6.0005, p. 16, capitalization in original.)

Dr. Hellstein believes the only explanation for the "explo[sion]" in the number of BON case reports is the concomitant rapid spread of bisphosphonate usage. (Exh. 6.0005, pp. 17–19.)

Dr. Hellstein's opinions are fully set forth in his expert report submitted herewith, and the Court's attention is directed to the following portions of his report and discovery deposition:

- Fosamax causes ONJ by suppressing osteoclast activity below the level needed to carry out repair. (Exh. 5.0005: 324:15–325:6.) Osteoclastic activity is a part of healthy bone turnover, and the disruption of bone turnover "appears to be the key in development of BON." (Exh. 6.0005, p. 27.) Dr. Hellstein explains that bisphosphonates are designed to "'home' in on areas of high metabolic turnover," particularly the jaws, and their properties lead them to bind to such areas for years. (Exh. 6.0005, pp. 21–22.) Because turnover is stalled, damage including ONJ readily occurs. (Exh. 6.0005, pp. 21-27.)

- Dr. Hellstein explains Fosamax's concentrated action on the jaws, rather than in other areas of the body, because turnover in a healthy jaw is 3-6 times that of a human femur, and even higher in the spongy bone surrounding the teeth. (Exh. 6.0006, p. 27.) The jaws are the "canary in the coal mine"—i.e., the first place you would expect to see damage like osteonecrosis. (Exh. 5.0005: 325:2–6.)

d. The Preeminent Expertise of the PSC's Oral Medicine Experts Strikingly Contrasts the Relative Lack of ONJ Expertise of Defendant's Oral Medicine Experts.

[redacted] Dr. Glickman admitted that he never heard of Dr. Eisenberg or Dr. Tomar, and has readily admitted that he is not even the most knowledge bisphosphonate-ONJ expert in his own department. (Exh. 4.0005: 135:1-135:24, 141:24-

[redacted]

143:9, 151:6-152:13, 205:4-212:10.) Likewise, Merck's physiology expert, Dr. David Dempster, carefully researched the available medical and dental literature and saw multiple articles by Drs. Goss, Marx, and Hellstein, but nothing from Drs. Glickman, Tomar, or Eisenberg. (Exh. 4.0003: 145:15-146:19.) Merck scientist Dr. Anne DePapp testified that she has kept abreast of the pertinent scientific literature relating to Fosamax and ONJ and has seen nothing from Drs. Glickman, Tomar, or Eisenberg. (Exh. 3.0004: 334:19-335:8.)

e. Dr. Etminan

In addition to the above oral medicine experts, who have all authored peer-reviewed studies demonstrating the link between Fosamax use and ONJ, plaintiffs have provided the Court with the expert testimony of pharmacoepidemiologist, Dr. Mahyar Etminan. He, too, has published a peer-reviewed article quantifying the association between osteonecrosis and Fosamax ingestion. (*J. Rheumatology* 2008:35:547-9, Exh. 2.0272).

Applying accepted epidemiological methodologies, methodologies which defendants' own experts admit to having used themselves, Dr. Etminan has also concluded to a reasonable degree of scientific certainty that Fosamax ingestion causes ONJ. Dr. Etminan engages in a Bradford-Hill analysis of the causation evidence and concludes that Fosamax does cause ONJ. (Exh. 6.0001:, pp. 10-20.)

ii. There Is an Association Between Fosamax and Osteonecrosis of the Jaws.

At pages 13 through 16 of its brief, Defendant argues that there is no statistically significant association between Fosamax and osteonecrosis of the jaw. But, as explained above, a statistically significant measured association is not required under *Daubert*. *See see also In re Neurontin*

Marketing Sales Practices, and Prods. Liab. Litig, - - - F.Supp.2d - - -, 2009 WL 1212944, *26 (D. Mass. 05/05/09) (finding that an FDA study showing a non-statisically significant association constituted evidence of an association). Further, Defendant's own experts recognize that Fosamax is associated with ONJ.

For example, upon reviewing his oral surgery department's website, Dr. Glickman agreed that Fosamax is associated with osteonecrosis of the jaws:

Q: You see there that heading that reads "Bisphosphonate Medications for Cancer Or Osteoporosis"?

A: Yes.

Q: That statement reads, "bisphosphonate medications (e.g., Zometa, Aredia, Fosamax) have been associated with a condition referred to as osteonecrosis of the jaws (ONJ) that involves a breakdown and death of jaw bones." Did I read that correcly?

A: You read it verbatim.

Q: Is that statement factually accurate?

A: That there's an association?

Q: Yes.

A: Yes.

(Exh. 4.0005: 132:24-133:16.). Similarly, Dr. Eisenberg testified as follows:

Q: Is there an association between bisphosphonates and ONJ, yes or no?

A: Yes.

Q: And that includes Fosamax; right?

A: Well, it's a bisphosphonate.

(Exh. 4.0004: 53:6-53:10.)

Additionally, the relatively recent ICD-9 code for "aseptic necrosis of the jaw" includes an e-code related to the oral bisphosphonate administration: "In the cases where a diagnosis of BRONJ is confirmed, there is a new ICD-9- CM code for aseptic osteonecrosis of the jaw, 733.45. There are also two new ICD-9-CM E codes, E933.6 and E933.7 to track the route of administration. E933.7 describes the use of bisphosphonates administered intravenously and E933.6 describes the oral administration of the drug." (http://www.aaoms.org/faq_coding.php, copy attached as Exh. 8.0004.)

iii. Multiple Incidence and Prevalence Studies Demonstrate an Increased Risk of Osteonecrosis of The Jaws in Fosamax Users.

At least three prevalence studies support the proposition that Fosamax is capable of causing ONJ in the general population.

The FDA-commissioned a study to for purposes of assessing the topic of bisphosphonate-induced ONJ. "In 2006, a unique collaboration was formed between Kaiser Permanente's Division of Research, Oral and Maxillofacial Surgery, and Pharmacy Outcomes Research Group, with support from the Food and Drug Administration, to determine the prevalence of this rare jaw complication among patients receiving oral bisphosphonate drugs. This collaborative effort resulted in the **P**redicting **R**isk of **O**steonecrosis with **B**isphosphonate Exposure (PROBE) Study." (Lo J, et al., "The Kaiser Permanente PROBE Study," *Kaiser Permanente Northern California Quarterly Newsletter: Research Update*, 2008; 10(2): 1, 16. Exh. 2.1016.) The PROBE investigators mailed 14,000 dental surveys to Kaiser members with a history of recent bisphosphonate use. "The PROBE Study is the largest cohort to date in which surveillance for ONJ has been systematically conducted." (*Id.* at 16.) Over 8,500 members returned the completed surveys to the study group, which then engaged in chart review and dental examinations of the responders with apparent ONJ. The PROBE

study determined a preliminary prevalence rate of 1 in 1,100, or 0.09%.

Dr. Goss' Australian study, was supported by the Australian health authority, ADRAC. (Exh. 2.0348.) The study investigators utilized denominator data provided to them by Merck, reported a maximum frequency of ONJ in patients receiving oral bisphosphonates as 1 in 950 and a minimum frequency as 1 in 2,030. For those Fosamax patients who have undergone dental extractions, the frequency rises to a maximum frequency of 1 in 125 and a minimum frequency of 1 in 270. Merck contributed data to this study which directly impacted and supported the conclusions reached on the incidence rate. (Exh. 1.0121, Exh. 5.0003: 36:11-38:11.)

Meanwhile, a recent study conducted out by the University of Southern California School of Dentistry revealed that even short-term use of Fosamax (defined as one year) led to ONJ in a certain subset of patients. (Sedghizadeh P, et al., "Oral bisphosphonate use and the prevalence of osteonecrosis of the jaw: An institutional inquiry," *J Am Dent Assn* 2009; 140:61-66, Exh. 2.0805.) The authors of the USC study found nine cases of ONJ among 208 patients with a history of Fosamax use. Of significance, no cases of ONJ were found among the13,522 patients without a history of Fosamax use (including 4,384 who underwent a dental extraction). The USC researchers concluded: "The findings from this study indicated that even short-term oral use of alendronate led to ONJ in a subset of patients after certain dental extractions were performed." (Exh. 2.0805, p. 61.)

What is remarkable about these studies is that there has been established no background rate for osteonecrosis of the jaw, absent the bisphosphonate patient population. Defendant's employees have repeatedly searched for such a background rate and have been unable to find one. (Exh. 3.0003: 344:3-347:3, Exh. 3.0005: 477:7-478:16.) [redacted]

[redacted]

As Dr. Hellstein explained, the prevalence studies give "you evidence of what is creating the risk" and the prevalence rates reported indicate an increased risk for osteonecrosis of the jaw from the oral bisphosphonates. (Exh. 5.0005: 84:1-86:9.)

iv. Case-reports and Case-series Constitute Epidemiology Supporting a Causal Relationship Between Fosamax and Osteonecrosis of the Jaws.

Contrary to Defendant's assertion that peer-reviewed case-reports and case-series have no value in assessing causality, they are a vital component of the empirical evidence an expert must consider when examining the relationship between an adverse event and a particular agent.

The Second Circuit has allowed expert testimony relying in part on published and unpublished case reports, as they provide additional support to meet the plaintiff's burden of establishing causation. *Zuchowicz,* 140 F.3d at 386; *McCullock*, 61 F.3d at 1044; *Becker*, 896 F. Supp. at 102. Courts elsewhere have held experts' testimony on causation admissible where their opinions were based in part on case reports and internal adverse event data. *Kennedy*, 161 F.3d at 1228; *Hopkins*, 33 F.3d at 1124-25; *Glaser,* 32 F.3d at 972; *Benedi*, 66 F.3d at 1384; *In re Neurontin Litig*, - - - F.Supp.2d - - -, 2009 WL 1212944, **28, 31; *In re Phenylpropanolamine (PPA) Litigation*, 289 F. Supp. 2d at 1242, 1246; *Tyler v. Sterling Drug, Inc.*, 19 F. Supp. 2d 1239, 1241 (N.D. Okl. 1998); *Brasher v. Sandoz Pharms. Corp.*, 160 F. Supp. 2d 1291, 1294 (N.D.Ala 2001); *Globetti,* 111 F. Supp. 2d at 1178.

As one court recently noted, "[c]ase reports and valid studies [that] have been published and subjected to peer review that suggest a plausibility of a causal link between a medical problem and a drug may be sufficient on their own, under certain factual circumstances, to meet *Daubert*. *Eve v. Sandoz Pharms. Corp.*, No. IP 98-1429-C-Y/S, 2001 U.S. Dist. LEXIS 4531, at *64 (S.D. Ind., Mar. 7, 2001) (Exh. 8.0008). Because case reports are reasonably reliable evidence under *Daubert* to satisfy the threshold requirement for admissibility, it is a question for the jury to decide what weight to give the evidence, and whether plaintiffs have met their burden of proof. *Id.* at 64 (citing *Tyler*). Moreover, case reports need not be accepted by a widespread majority of the scientific community as long as they represent the view of a significant minority. *Rogers v. Sec'y of Health & Human Servs.*, 2000 WL 1337185, *14 (Fed. Cl. 2000). (Exh. 9.)

The use of case reports in medicine is longstanding and vital, as evidenced by the continued publication of such reports in peer reviewed scientific journals. REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, *supra*, 633-34 (Exh. 8.0001) (including case reports as evidence in analyzing general causation). The typical published case report describes the patient, her individual circumstances of exposure, the onset of the injury, and the plausibility of the link between exposure and disease. In comparison, an epidemiologic study defines a group of subjects, their circumstances of exposure, their patterns of disease, and then considers the plausibility of these total patterns. Epidemiologists consider case reports relevant to the "totality" of the data when assessing causation. *See Ambrosini,* 101 F.3d at 136 (expert looked at the entire medical literature, including published case reports for consistency of data). The REFERENCE MANUAL is instructive:

> Case reports lack controls and thus do not provide as much information as controlled epidemiological studies do. However, case reports are often all that is available on a particular subject because they usually do not require substantial, if any, funding

> to accomplish, and human exposure may be rare and difficult to study. Causal attribution based on case studies must be regarded with caution. However, such studies may be carefully considered in light of other information available, including toxicological data.

REFERENCE MANUAL, *supra,* at p. 634 (emphasis added) (Exh. 8.0001). Here, plaintiffs reinforce their opinions that Fosamax can cause the injuries alleged with case reports published in the peer-reviewed medical literature, in addition to numerous adverse event reports. Moreover, plaintiffs' experts do not rely solely on case reports to support their conclusions. Rather, these case reports provide additional, consistent evidence of causation.

Although case reports do not provide as much information as controlled epidemiology studies do, they are scientific evidence nevertheless, and add to the totality of the evidence. *Id.* The published case reports typically contain detailed information, and the authors conducted a careful differential diagnosis to rule out other likely causes of disease. In determining the etiology of their patients' disease, the authors also employed the same methodology that plaintiffs' experts did in assessing causality: they conducted a thorough search of the worldwide medical literature, including case reports, clinical studies, animal studies, and pharmacology. "Differential diagnosis, or differential etiology, is a standard scientific technique of identifying the cause of a medical problem by eliminating the likely causes until the most probable one is isolated." *Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 262 ((4th Cir. 1999). Searching the literature for likely causes is part of the differential diagnosis methodology. *Benedi*, 66 F.3d at 1384 ("We will not declare [differential diagnosis, including a search of the peer-reviewed literature] invalid and unreliable in light of the medical community's daily use of the same methodologies in diagnosing patients."); *Perkins,* 299 F. Supp. 2d at 57 (differential diagnosis is a technique that has widespread acceptance in the medical

community); *Baker v. Dalcon Shield Claimants Trust*, 156 F.3d 248, 252 (1st Cir. 1998) (same)

In this case, as Dr. Etminan has explained, the existence of the case reports is of particular utility given the lack of the background rate of osteonecrosis of the jaw in bisphosphonate-naive patients: "Other than radiation-induced osteonecrosis of the jaw, when one reviews the available medical and dental literature relative to the occurrence of osteonecrosis of the jaw, or analogs of the event, the event is very rarely reported and the evidence demonstrates that the previously reported events usually had resolution which is atypical of the current situation with bisphosphonate-induced osteonecrosis of the jaw." (Exh. 6.0001: p. 18.) Dr. Etminan's assessment is shared by Merck's Dr. Kimmel. [redacted]

As Dr. Etminan reports, there are hundreds of published case reports and series attributing osteonecrosis of the jaw to bisphosphonate use, including Fosamax. A good representative sampling of these articles include the following:

- Krueger CD, West PM, et al. "Bisphosphonate-induced osteonecrosis of the jaw." *Ann Pharmacother* 2007; 41:276-84 (a review of the case reports and case series) (Exh. 2.1017)
- Farrugia, MC, Summerlin DJ. " Osteonecrosis of the mandible or maxilla associated with the use of new generation bisphosphonates." *Laryngoscope* 2006;116:115-20 (Exh. 2.0003)
- Marx RE, Sawatari Y, Fortin M, Broumand V. "Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the Jaws: Risk Factor, recognition, prevention and treatment." *J Oral Maxillofac Surg* 2005;63:1565:1575 (Exh. 2.0005)
- Hellstein JW, Marek CL. "Bisphosphonate osteochemonecrosis (bis-phossy jaw): is this phossy jaw of the 21st century?" *J Oral Maxillofac Surg* 2005;63:682-89 (Exh. 2.0245)

- Migliorati CA, Schubert MM, Peterson DE, Seneda LM. "Bisphosphonate-associated osteonecrosis of the mandibular and maxillary bone." *Cancer* 2005;104:83-93 (Exh. 2.0481)

- Yarom N, Yahalom, et al., "Osteonecrosis of the jaw induced by orally administered bisphosphonates: incidence, clinical features, predisposing factor and treatment outcome." *Osteoporos Int* 2007; 18:1363-1370 (Exh. 2.1018.)

Of greater significance is the largest case-series in the world: Merck's internal adverse event data relating to Fosamax and osteonecrosis of the jaws. [redacted]

While Merck's expert Dr. Bilezikian agreed that "someone who is prescribing the drug such as Fosamax really would like to know how many adjudicated cases there are of an adverse event like osteonecrosis of the jaw in association with a drug which that clinician is prescribing," (Exh. 4.0001: 194:19-195:2), Merck has never disclosed publicly these numbers.

v. It Is Biologically Plausible That Fosamax Can Cause Osteonecrosis of the Jaws.

Biological plausibility is defined as the consideration of existing knowledge about human

biology and disease pathology to provide a judgment about the plausibility that an agent causes a disease. REFERENCE MANUAL. p. 535. (Exh. 8.0001). Defendant's argument attempts to pursuade this Court that the mechanism of action must be proved with scientific certainty. This opinion is inharmonious with basic scientific principles and *Daubert*. *In re Phenylpropanolamine (PPA) Litig.*, 289 F.Supp.2d at 1247 (quoting *Daubert*, 509 U.S. at 590) (observing that putative mechanism of injury need not be shown with certaintly as "'arguably there are no certainties in science.'") This is why it is called biologic plausibility rather than biologic certainty, and"[w]hen biological plausibility exists, it lends credence to an inference of causality." REFERENCE MANUAL, *supra,* at p. 522 (Exh. 8.0001). Furthermore, "when the relative risk is much smaller, or when there is no epidemiological evidence at all, biological plausibility becomes much more important." *Id.*; *see also In re Neurontin Litig*, - - - F.Supp.2d - - -, 2009 WL 1212944, *26 (expert's reliance in part on biologic plausibility constituted "good grounds" to support a causal relationship opinion).

Merck's own expert, Dr. John Bilezikian, illustrates this point. He testified that it is not really known with certainty how or why Fosamax works to prevent bone fractures; there are plausible mechanisms but not have been proven with certainty. (Exh. 4.0001: 52:10-55:7, 57:1-59:12, 62:16-64:7, 123:19-124:22.) Courts have found biological plausibility a scientifically reliable methodology supporting experts' opinions regarding general causation, particularly where it is consistent with other available data. *See In re Phenylpropanolamine (PPA) Litigation*, 289 F. Supp. 2d at 1246 (neurologist expert's testimony that PPA could cause ischemic strokes was admissible based on biological plausibility and other nonepidemological sources); *Ambrosini*, 101 F.3d at 136 (epidemiologist's reliance on biological plausibility and other consistent lines of evidence was held to be scientifically reliable); *Becker*, 896 F. Supp. at 101 (expert's testimony was admissible based

in part on the known pharmacologic actions of active ingredients of dietary supplement). Defendant's argument that biologic plausibility must be proven irrefutably is disingenuous and contrary to well established legal authority.

a. Fosamax Massively Suppresses Bone Turnover.

If anything is certain in this litigation it is that Fosamax massively suppresses bone turnover.

Fosamax is designed as an "anti-resorptive" agent. Human bones are constantly purged and remodeled by the cells known as osteoclasts and osteoblasts. Osteoclasts cause bone "resorption": i.e., they remove tired, dead, infected, or compromised bone tissue and dispose of it. Osteoblasts then lay down new bone to replace the removed bone. When the old bone tissue is removed by osteoclasts, new healthy bone is built in its stead by osteoblasts. This process is known as bone remodeling. (Exh. 6.0006: pp.5-6.)

The process by which Fosamax works to prevent osteoporosis is through the inhibition of osteoclasts; by inhibiting osteoclasts, bisphosphonates inhibit bone material from being resorbed (or removed) by osteoclasis. (Exh. 2.0003, p.115; Exh. 2.0371, pp. 2692-93.) "However, normal osteoclasis is vital to bone turnover and bone viability. . . . Interruption of this homeostatic cycle by overly effective inhibition of bone resorption results in the accumulation of nonvital osteocytes and micro fractures of the old mineral matrix." (Exh. 2.0251, p. 1115.)

There is little debate in the scientific community about the mechanism of actions of bisphosphonates. In the article, *Bisphosphonate: Mechanism of Action* , Merck scientist Gideon Rodan, with the assistance of Professor Herbert Fleisch wrote: "At the tissue level, the action of all active bisphosphonates appear to be similar: a reduction in bone turnover. This is evidenced by a decrease in both bone resorption and bone formation, as evidenced by biochemical markers."

(Exh. 2.0371, p. 2692.) [redacted] Dr. Bilezikian testified there are several different ways to measure bone turnover, including biopsy samples as well as serum and urine surrogate markers; from an accuracy standpoint, the most desired data for measuring bone turnover is the biopsy, although this is difficult to get because of the invasive nature of the testing and so it is only done in the research setting, rather than the clinical setting. (Exh. 4.0001: 131:21-136:1.) Merck's own testing reveals that, based upon bone histomorphometry (biopsy) data, Fosamax suppresses bone turnover by 94% in Fosamax patients and 98% in those patients who are on Fosamax and hormone replacement therapy, although no warning is given as to the potential for any undesired side effects. (Exh. 1.0019, p. 9.) [redacted]

Dr. Bilezikian testified that, of all the oral bisphosphonates, Fosamax suppresses bone turnover the most. (Exh. 4.0001: 122:4-122:8.) Fosamax induces maximum bone suppression within three to six months of therapy. (Exh. 4.0001: 162:1-163:17.) While Defendant has attempted to color its bone turnover suppression data to infer that it simply reduces bone turnover to a

premenopausal reference range, the data show that, when measured by CTX serum laboratory values, the scores are less than 1/2 the premenopausal mean, falling below even the multiple standard deviation reference range. [redacted]

b. The Massive Suppression of Bone Turnover Is the Plausible Mechanism for ONJ Induced by Fosamax.

Oral surgeons and dentists alike, including Merck's dentist/bone physiologist Dr. Kimmel, recognize the likely mechanism for Fosamax's ability to induce ONJ is the massive suppression of bone turnover (which Fosamax is designed to effect).

1. The PSC's Experts Reliably Explain That the Likely Mechanism of Action for the Induction of ONJ by Fosamax Is the Massive Suppression of Bone Turnover.

Long before they were retained in this litigation, Plaintiff's oral medicine experts had presented in peer-reviewed medical journals their opinions that bisphosphonate's ability to induce ONJ likely was a result of the suppression of bone turnover. These experts' opinions are reflected in the oral surgery community. In a very recent publication in the *Journal of Oral and Maxillofacial Surgery*, Drs. Allen and Burr (whose animal research is discussed below) presented the following conclusions:

- Nearly every report and review of bisphosphonate related osteonecrosis of the jaw ("BRONJ") points to bisphosphonate-induced remodeling suppression as a likely mechanism of action;
- There is no doubt that bisphosphonates suppress bone remodeling; and
- It is clear that bone remodeling is considerably higher in the jaw compared with other skeletal sites, as much as 10 to 20 times higher.

(M. Allen; D. Burr, "The Pathogenesis of Bisphosphonate-Related Osteonecrosis of the Jaw: So

Many Hypotheses, So Few Data", *J Oral Maxillofac Surg* 67: 61-70, 2009, Suppl 1, Exh. 2.1002.)

These statements are in accord with the opinions expressed by PSC's experts. Recent peer-reviewed publications by two of the PSC's experts are also consistent with the conclusion that bisphosphonate-induced remodeling suppression is the likely mechanism of action. (R. Marx; J. Cillo; J. Ulloa, "Oral Bisphosphonate-Induced Osteonecrosis: Risk Factors, Prediction of Risk Using Serum CTX Testing, Prevention, and Treatment,*J Oral Maxillofac Surg*65: 2397-2410, 2007 (Exh. 2.0252; R. Kunchur; A. Need; T. Hughes; A. Goss, "Clinical Investigation of C-Terminal Cross-Linking Telopeptide Test in Prevention and Management of Bisphosphonate-Associated Osteonecrosis of the Jaws," *J Oral Maxillofac Surg* 67: 1167-1173, 2009, (Exh. 2.1003.) Both of these publications discuss the use of C-terminal cross-linking telopeptide test (CTX test) in the prevention and management of osteonecrosis of the jaws in patients taking bisphosphonates. When bone turnover is decreased by a bisphosphonate, the CTX value is low.

In the Marx study the authors investigated 30 consecutive cases of osteonecrosis of the jaw which met the definition (AAOMS Task Force) of bisphosphonate-induced osteonecrosis. A detailed history was taken from each patient and each patient underwent a fasting morning blood draw for a CTX bone turnover marker assessment as part of their regular osteoporosis follow-up. Seventeen of the 30 patients in the study were still taking their bisphosphonate at the time they entered the study. These patients stopped their bisphosphonates upon entry into the study. After a six month of drug cessation (dechallenge), each of these patients showed a direct and significant improvement in the CTX values. This improvement correlated to either a spontaneous resolution of the exposed bone, a significant improvement in the amount of exposed bone or an uncomplicated healing response following surgery. .

Dr. Goss replicated Dr. Marx's finding in his case-control CTX study. In the Goss CTX study, 348 patients underwent a fasting morning CTX test. Two hundred twenty-two of the patients were at risk for osteonecrosis of the jaw (ONJ) who had been referred for extractions, 15 had ONJ and 113 were controls. Consistent with the Marx study, the authors found that all patients taking bisphosphonates have a low CTX value. Also consistent with the Marx study, the authors found that following drug cessation, a return to more normal bone turnover occurs. Thus, there is robust scientific data supporting the expert's opinions relating to the relationship between Fosamax's suppression of bone turnover and osteonecrosis of the jaw. The evidence demonstrates a biologically plausible mechanism of action, and the PSC's experts properly relied upon these data.

2. Merck's Own Bone Physiologist Shares the PSC's Experts' Impressions about Suppression of Bone Turnover Insofar as it Related to Onj.

A court may consider a company's internal consideration of the putative mechanism of action when addressing a *Daubert* challenge to the opponent's expert evidence. *In re Neurontin*, - - - F.Supp.2d - - - 2009 WL 1212944 at *26.The oversuppression of turnover mechanism discussed by the PSC's experts, and supported by their studies, is well accepted as the most likely mechanism of action for the onset of bisphosphonate-related ONJ. Merck's own Dr. Kimmel presents the same scientific opinions as those presented by the PSC's experts.

[redacted]

[redacted]

[redacted]

[redacted] Similarly, Defendant's oral pathology expert, Dr. Eisenberg testified that, in rare cases known as osteopetrosis, dead jaw bone results from the suppression of the osteoclastic process. (Exh. 4.0004: 234:21-236:12.)

This is not junk science. This is the plausible explanation of how Fosamax causes ONJ.

vi. Animal Studies Support the Scientific Conclusion That Bisphosphonates and Specifically Fosamax Can Cause Osteonecrosis of the Jaws in

Humans.

a. Animal Studies Are Reliable, Admissible Evidence Supporting an Expert's General Causation Opinion.

Plaintiffs' experts also rely on published, controlled animal studies, an additional line of evidence to support causation. Animal studies are conducted for the purpose of extrapolating results and generating a biologically plausible hypothesis to test in humans. Defendant claims that animal studies alone are not admissible because animals cannot be reliably compared to people. Here, however, other lines of evidence show that Fosamax can cause similar injuries in animals and people, at both higher and recommended doses. Therefore, the animal studies with bisphosphonates provide additional confirming evidence that Fosamax is capable of causing the injuries at issue.

Toxicology based on animal studies ("in vivo") is helpful to assess toxicity in humans. *See* REFERENCE MANUAL at p. 553-55 (Exh. 8.0001). Animal studies often provide useful information about pathological mechanisms. *Id.* at 555. Toxicological research (including both animal studies and chemical/structural correlations) provides much of the basis for scientific judgments relating toxic exposures to health effects. *Id.* This is especially true in instances where it is impossible to conduct such studies in humans. *Id.* at 592 n. 81.

Courts have long recognized the usefulness of animal tests. "There can be no dispute that properly designed and conducted animal testing can yield relevant and useful information in the field of human toxicology." *Bourne v. Dupont De Nemours & Co., Inc.*, 189 F. Supp. 2d 482, 498 (S.D.W.V. 2002) (citing *Turpin v. Merrell Dow Pharms., Inc.*, 959 F.2d 1349, 1360-61 (6th Cir. 1992)). "Animal studies often comprise the backbone of evidence indicating biological hazards, and their legal value has been recognized by federal courts and agencies." *Id.* The Ninth Circuit held

that it was an abuse of discretion for the trial court to exclude defense expert testimony on causation based on animal studies merely because of a species gap or difficulty in extrapolation to humans. *See Metabolife International, Inc. v. Wornick*, 264 F.3d 832, 842 (9th Cir. 2001); *In re Phenylpropanolamine (PPA) Litigation*, 289 F. Supp. 2d at 1242, 1247 (expert testimony admissible based on animal studies and other non-epidemiological evidence); *Globetti*, 111 F. Supp. 2d 1174 (animal studies and other data are all recognized and accepted scientific methodologies for assessing causation); *In re Neurontin Litig.*, 2009 WL 1212944, at *34 (expert's reliance on animal studies and mechanism of action theory rested on "good grounds" and was therefore admissible). Here, multiple lines of medical evidence and clinically relevant animal studies all point in the same causal direction. Thus, animal studies are another consistent and valid line of evidence upon which plaintiffs' experts may reasonably rely.

Consistent with legal authority, there is consensus among practicing scientists that making a causal inference requires looking at the totality of the evidence, and in doing so, making sure that each piece of the puzzle fits with the others.[13] Science tells us that animal studies, conducted upon the appropriate animal models, constitute an important element of a general causation assessment.

As Dr. Etminan explains, "Animal studies are useful data because a scientist, through controlled and typically high-dose models, can seek to induce adverse events and thereby study biologic plausibility, whereas such a study could not be conducted with human studies." (Exh. 6.0001: p. 14). Animal studies allow scientists to conduct experiments and gather data that cannot be done or gathered with humans. Accordingly, animal studies form one of the bases for pharmaceutical drug testing and development, including at Merck. (Exh. 3.0006: 54:20-57:2.)

[13] Exh. 8.0005 - ROTHMAN, KENNETH J., and SANDER GREENLAND, *Chapter2, in* MODERN EPIDEMIOLOGY, 16 (Lippincott, Williams & Wilkins 2d ed., 1998)

The multiple animal studies relied upon by the PSC's experts were done so using the most reliable animal models. The results from these studies "fit" consistently with the other pieces of the causation puzzle, and support the opinions and methodology of plaintiffs' experts in this litigation. Combined with all of the other evidence, these animal studies constitute a valuable and relevant "piece" of the causation puzzle.

b. The Bisphosphonate Animal Studies at Issue Were Conducted upon the Most Reliable Animal Models: Rat and Dog.

Dr. Kimmel is the Director of Animal Research in Merck's Department of Molecular Endocrinology. (Exh. 3.0006: 45:18-46:4.) Dr. Kimmel testified that the best animal model for studying bisphosphonates is the rat. (Exh. 3.0006: 47:21-51:1.) Dr. Kimmel further testified that dogs are also reliable as a testing model for the human skeleton relative to bone research. (Exh. 3.0006: 80:9-81:14). This testimony is noteworthy because each of the animal studies referenced were conducted on rats or dogs.

Dr. Kimmel's testimony about the relevance of bisphosphonate-related rat and dog animal studies is no surprise considering his past writing on the subject. [redacted]

[redacted] He further testified in his deposition that "[t]here's quite a bit of data out there -- or 'out there,' I mean in the published literature, where the results that you get from dog studies that one obtains from dog studies are the same as what one obtains in studying humans." (Exh. 3.0006: 79:18-80:8.) Thus, Merck's own scientists agree with the PSC's experts that, methodologically, it is appropriate to extrapolate the results of animal studies on bisphosphonates to humans.

c. The 1981 Gotcher Clodronate Rat Study Shows Bisphosphonates Are Capable of Causing Osteonecrosis of the Jaw.

From 1976 to 1978, Dr. Jack Gotcher and Dr. Webster Jee studied the effects of the bisphosphonate, clodronate, on the jaws of rats. (Exh. 4.0006: 18:19-22:5). In 1981 their study was peer reviewed and published in the Journal of Periodontal Research. (Exhibit 2.0144). Drs. Gotcher and Jee were able to induce exposed, sclerotic bone in the group of rats treated with 18 weeks of bisphosphonate treatment. Conversely, the control group (which received no bisphosphonate treatment) did not show any exposed or sclerotic bone. (Gotcher J, Jee W, "The Progress of the Periodontal Syndrome in the Rice Rat: II. The Effects of a Diphosphonate on the Periodontium" *J. Periodontal Res.*, 1981; 16: 441-445, Exh. 2.0144.). Stated simply, this study showed that bisphosphonates can cause ONJ in rats.

Aside from its highly probative findings, this study is particularly relevant for two different reasons: 1) Dr. Kimmel worked with Dr. Gotcher and Dr. Jee at the University of Utah from 1976 to 1978 and was aware of this research (Exh. 4.0006: 22:6-25:18; Exh. 3.0006: 31:21-32:13), and 2) Dr. Gotcher, is one of Merck's consultants. [redacted]

[redacted]

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[redacted] This rat study conducted by Dr. Gotcher demonstrated, nearly 30 years ago, that bisphosphonates can cause ONJ. Further, it is evidence that Merck knew or should have known of the potential for bisphosphonates to cause ONJ as early as 1997 (when Dr. Kimmel started at Merck) and as late as 2005 (when Dr. Gotcher told Merck directly).

d. The Vignery-Baron Rat Study Shows That the Jaw Has a High Bone Turnover and Bisphosphonates Have an Affinity for Bones with High Turnover.

In 1980, Drs. Vignery and Baron, from the Yale School of Medicine, wrote a peer reviewed article titled "Comparative Effects of APD and Cl_2MDP [bisphosphonates] on Bone in the Rat: In Vivo and In Vitro Studies", *Metab. Bone Dis. Rel. Res.*, 1980, Vol. 2: 381-387, (Exh. 2.0162). Drs. Vignery and Baron were described by Dr. Kimmel as "... highly respected professionals within our -- within the bone research field." (Exh. 3.0006: 425:13-425:21)

This 1980 rat study measured the relative differences of turnover throughout the body's skeleton, and showed that one of the areas of highest bone turnover was the mandible. . The following quote summarizes the pertinent findings of this study: "Even though rat tail vertebrae

undergo complete remodeling sequences along their endosteal trabecular surfaces, as in the adult human, none of the diphosphonates tested at any dose induced any noticeable changes in any of the bone remodeling parameters after 10 days of treatment. However, looking at the rapid turnover type of bone, i.e., the alveolar [jaw] bone, marked changes are observed." (Exh. 2.0162, p. 382.)

The 1980 study was prescient: "In the present study we used in vivo and in vitro techniques to analyze and compare the effects of [diphosphonates] on bone resorption and bone formation. The data presented here confirm previous results showing that disphosphonates are potent inhibitors of bone resorption, but interfere also with bone formation. However, the present experiment brings up new information about the relationship between a given dose of diphosphonate and its direct effect on bone according to the turnover rate of the bone." (Exh. 2.0162, p. 384.) As Professors Vignery and Baron observed, the alveolar bone in the jaw was unique in its response to the bisphosphonate administration: "While none of the doses tested had any measurable effect on the trabeculae of the vertebrae, all of the doses induced an inhibition of bone resorption with or without an inhibition of bone mineralization in the alveolar [jaw] bone." (Exh. 2.0162, p. 386.)

This animal study conducted by highly respected bone scientists provides further proof that the jaw is one of the body's highest areas of bone turnover. Dr. Kimmel testified that he has not seen any piece of work contradicting the conclusions of this study. (Exh. 3.0006: 432:23-433:34) Moreover, Dr. Kimmel admits that this finding is important because bisphosphonates have an affinity to areas of high turnover. (Exh. 3.0006: 432:3-433:19.) This is no surprise to Merck, as it is well known by Merck scientists that alendronate does not distribute evenly througout the skeleton and binds preferentially to bones with high turnover rates. (Exh. 3.0006: 447:1-448:4.) Thus, because the jaw is one of the body's highest areas of bone turnover and because bisphosphonates

have an affinity to areas of high bone turnover, it is "biologically plausible" that Fosamax will affect the jaw greater than other areas of the body.

e. The Allen-Burr Dog Study Shows That Fosamax Treatment Causes Mandible Matrix Necrosis.

In 2008, the Journal of Oral Maxillofacial Surgery published a peer reviewed animal (dog/beagle) study article by Dr. Matthew Allen and Dr. David Burr titled "Mandible Matrix Necrosis in Beagle Dogs After 3 Years of Daily Oral Bisphosphonate Treatment," *J Oral Maxillofac Surg,* 2008; 66(5):987-994, (Exh. 2.1004). Impetus for this study and article was the increasing number of ONJ cases among bisphosphonate users.

The specified purpose of this beagle study was stated by the authors as follows: "An increasing number of reports have implicated bisphosphonates as contributing to osteonecrosis. The goal of this study was to evaluate mandible necrosis in beagle dogs treated for 3 years with oral alendronate (ALN) [Fosamax]." (Exh. 2.1004, p. 987.) The researchers concluded: "Three years of daily oral bisphosphonate [specifically Fosamax] treatment reduces bone turnover significantly and increases the incidence of matrix necrosis within the mandible of dogs." (*Id.*) Dr. Kimmel's writings and testimony on the subject directly support the reliability of this beagle study. Dr. Kimmel testified that the beagle is the most reliable species of dog for studying the effects of bisphosphonates. (Exh. 3.0006: 81:22-82:8).

This study, its conclusion and findings provide support for the "biologic plausibility" of plaintiffs' general causation theories and expert opinions for as Dr. Hellstein described the body. It provides additional support for other Bradford Hill criteria including: a) Temporal Relationship, b) Strength of Association, c) Dose-Response, and d) Specificity. Considering the fact that Fosamax

was the specific drug with which these beagles were tested, it is inappropriate for Defendant to argue that this study is not probative and relevant.

f. The Recent Hikita Study Shows That Fosamax Impairs Initial Healing of the Tooth Extraction Socket.

The Court can confirm the reliability of the animal studies relied upon by the PSC's experts as a result of a very recent rat study relating to alendronate and delayed jaw healing. In March of 2009, another animal (rat) study was published titled "Bisphosphonate administration prior to tooth extraction delays initial healing of the extraction socket in rats," *J Bone Miner Metab* (in press, published on-line, May 13, 2009), (Exh. 2.1005). Impetus for this study and article was the increasing number of ONJ cases among bisphosphonate users who have had tooth extractions. (Exh. 2.1005, p. 1.).

The researchers studied the effects of alendronate on extraction socket healing in rats that were pretreated with alendronate prior to tooth extraction." (Exh. 2.1005, p. 1.) The control group rats were given a physiological saline (rather than alendronate) two days prior to teeth (maxillary right second molars) being extracted. The experimental group rats were treated with alendronate two days before and after their teeth (maxillary right second molars) were extracted. Notably, the conditions of the experimental group rats mirrored the same pharmacological and medical conditions that many of the plaintiffs in this litigation experienced – tooth extraction after the administration of Fosamax.

The results of the study indicated "... that alendronate [Fosamax] directly affects osteoclast function with respect to healing of the extraction socket, given the observed delayed healing." (Id. at p. 8 of the article). This study concluded that "... administration of alendronate [Fosamax] to rats

before tooth extraction initially inhibited bone resorption in the extraction socket. This delay in initial healing of the extraction socket may be involved in the development of BRONJ." (Id. at p. 9 of the article). This most recent study is excellent confirmatory evidence of all the other factors discussed and relied upon by the PSC's experts.

g. The 2002 Astrand Rat Study Shows That Once the Necrotic Bone Exists, Fosamax Prevents it from Being Resorbed.

In 2002, an animal (rat) study article was presented by Dr. Jorgen Astrand and others "Systemic alendronate prevents resorption of necrotic bone during revascularization. A bone chamber study in rats," *BMC Musculoskeletal Disorders* 2002, 3:19-24 (Exh. 2.1006). The results of this study were that "[i]n rats treated with alendronate the necrotic bone was not resorbed, whereas it was almost entirely resorbed in the controls." (Exh. 2.1006, p. 1.) The conclusion of the study was that: "Systematic alendronate [Fosamax] treatment prevents resorption of necrotic bone during revascularization.." (Exh. 2.1006, p. 1.) This is further evidence, available to Merck in 2002, that Fosamax would impair the removal of dead, diseased, and compromised bone in the jaw.

vii. Other Nitrogenous Bisphosphonates Have Been Shown to Cause Osteonecrosis of the Jaws.

Plaintiffs' experts base their opinions that Fosamax can cause the injuries at issue in part on its similarities in both structure and pharmacological action to other bisphosphonates also known to cause ONJ. Courts have held that expert testimony based in part on evidence of similar drugs is admissible. *Kennedy,* 161 F.3d at 1230-31 (9th Circ. 1998); *In re Phenylpropanolamine (PPA) Litigation*, 289 F. Supp. 2d 1230 (noting that scientific literature also supports the practice of comparing PPA to other sympathomimetics, such as amphetamines); *Globetti*, 111 F. Supp. 2d at 1179; *Brasher*, 160 F. Supp. 2d 1291. In *Brasher,* the court stated, "There can be little question that

scientists use animal studies, case reports, and pharmacological comparisons of similar classes of drugs to infer conclusions, which are expressed in peer-reviewed journals and textbooks." *Id.* at 1296.

Comparison of similar drugs is a well-accepted scientific methodology. It is routinely used by clinicians, among other tools, in assessing whether a chemical agent is capable of causing a given disease. Here, the analogy of Fosamax to closely related bisphosphonates is one of several sources of evidence plaintiffs' experts rely upon in support of their opinions. It is consistent with those other lines of evidence and meets *Daubert's* threshold for admissibility. Differing conclusions by defense experts on the similarity of Fosamax to other bisphosphonates merely go to the weight of the evidence, not its admissibility. *McCullock,* 61 F.3d at 1044.

C. DEFENDANT INCORRECTLY CLAIMS THAT THERE IS A LACK OF GENERAL CONSENSUS RELATING TO FOSAMAX'S ABILITY TO CAUSE OSTEONECROSIS OF THE JAWS.

It is generally accepted within the fields of dentistry, oral surgery, pharmacology, toxicology and oncology that Fosamax can cause ONJ.

i. Illustrative medical textbooks reflect the consensus that bisphosphonates cause ONJ and the likely mechanism thereof.

In addition to Dr. Marx's text, other medical textbook are replete with these references, which have never been criticized or retracted. For example, in*Primer on Metabolic Bone Diseases and Disorders of Mineral Metabolism*, 7th ed., an Official Publication of the American Society for Bone and Mineral Research, Ch. 107, pp. 505-508: "Bisphosphonate-Associated Osteonecrosis of the Jaws" (Exh. 2.1007), included the following information for bone metabolism clinicians: "The strong association between bisphosphonate use is now well accepted", p. 505, and the

"etiopathogenesis has been attributed to suppression of bone turnover (caused by bisphosphonate-induced osteoclast inhibition) coupled with conditions that are unique to the mandible and maxilla", p. 505, (Exh. 2.1007). Additionally, in J.W. Little, et al., *Dental Management of the Medically Compromised Patient* 7th ed., Mosby Elsevier Publishing, pp. 447-449: "Bisphosphonate-Associated Osteonecrosis of the Jaws", the authors told dentists and oral surgeons:

- "BON can occur with the oral administration of bisphosphonates but is rare. In contrast, BON is a much more common complication of injected bisphosphonates." (*Id.* at 448.)
- "Physiologic microdamage and microfractures occur daily in the oral cavity. It is theorized that ina patient who is taking a bisphosphonate, result microdamage is not repaired, thus setting the stage for oral osteonecrosis to occur. Therefore, BON results from a complex interlay of bone metabolism, local trauma, increased demand for bone repair, infection, and hypovascularity." (*Id.*)

(Exh. 2.1008.)

One of the factors set forth under *Daubert* to consider the reliability of expert testimony is whether a particular technique or theory has gained "general acceptance" in the relevant scientific community. *Daubert*, 509 U.S. at 593-94. Textbooks are recognized as accepted scientific methodologies used for assessing the possible side effects and hazards associated with particular drugs and the causes of disease. *Globetti*, 111 F. Supp. 2d at 1178; *In re Phenylpropanolamine (PPA) Litigation*, 289 F. Supp. 2d at 1242. In *PPA*, the court noted, "While not conclusive, the multitude of textbooks and treatises including PPA as a risk factor for strokes adds to the reliability of plaintiffs' experts' opinions." *Id.*

ii. The Position Papers Presented by Defendant Do Not Undermine the General Acceptance of Bisphosphonates' Ability to Cause ONJ.

Defendant cites several position papers or consensus statements, but certainly omit several important ones from prominent medical societies, including the American Academy of Oral Medicine, and the American Academy of Endodontists, which clearly opine the bisphosphonates are a risk factor osteonecrosis of the jaw. However, the very nature of a "consensus" paper must be addressed as they are results of political compromise and conduct no new research in and of themselves.

For instance, when considering the ASBMR Task Force Report, Dr. Bilezikian testified that consensus papers or task force reports do not purport to speak for the membership of that particular medical society. (Exh. 4.0001: 213:8-213:20.) Consider the following testimony from Dr. Bilezikian about the AAOMS 2009 Position Paper and the ASBMR Task Force Report:

Q: Now, in paragraph 38 [of your report], you talk about the American Academy [sic] of Oral and Maxillofacial Surgeons 2009 update of their task force report. Do you find that task force report to be authoritative on the topic of bisphosphonates and osteonecrosis of the jaw?

A: It is a good paper.

Q: Do you consider it to be authoritative?

A: It is from that society, and it is a pretty good paper.

Q: Okay. You use the term "pretty good"?

A: Well, I mean, they are all - - you know, they're all one way or another. I mean, you could criticize the ASBMR task force, too. Task forces are very - - they're problematical because you have to take into account 800 authors. So, that's what I was saying. It is a compromise. A lot of this is a compromise.

Q: It is a political process at the end of the day, right?

A: I wouldn't use the term "political", but I think it is a compromise of views. That's what I would say.

Q: . . . And you would expect that to be true with this position paper, as with any other medical society's position paper, right?

A: I agree.

(Exh. 4.0001: 211:10-212:21.) Similarly, Dr. Eisenberg refused to identify the AAOMS position paper as "authoritative" (Exh. 4.0004: 90:25-91:6) and Dr. Glickman testified it was "suggestive, not authoritative". (Exh. 4.0005: 86:11-87:17.)

On page 13 of its brief, Defendant cites the following sentence from the AAOMS 2009 Position Paper: "the current level of evidence does not fully support a cause-and-effect relationship between bisphosphonate exposure and necrosis of the jaw." Dr. Bilezikian, reviewing the AAOMS paper as a scientist, rather than as a lawyer, agreed that one cannot infer from the paper that theAAOMS believes that bisphosphonates do not cause ONJ:

Q: Because nowhere in there do they say bisphosphonates do not cause ONJ, do they?

A: That's correct.

Q: And, in fact, the rest of the paper goes on to tell you how to treat bisphosphonate-related ONJ, right?

. . .

A: There is a therapeutic section here. That's correct.

Q: About bisphosphonate-related ONJ, right?

A: Yes, correct.

Q: And we really don't know what the authors mean in that particular sentence when they say, "The current level of evidence does not fully support a cause and effect relationship between bisphosphonate exposure and osteonecrosis of the jaw." If the standard is more likely than not, we don't know whether the particular authors considered that standard on the topic of the cause and effect relationship between bisphosphonate exposure and osteonecrosis of the jaw, right?

. . .

A: We're left with the sentence.

Q: And it's a poorly worded sentence, would you agree with me?

A: It's a sentence that has several interpretations.

. . .

Q: Someone can look at that sentence and come up with diametrically opposed interpretations as to what it means, right?

. . .

A: I suppose this could lead to a major difference of opinion.

(Exh. 4.0001: 215:9-217:14.)

Further, Defendant fails to mention that the two most prominent members of AAOMS, Dr. Robert Marx, and Dr. Sal Ruggiero (the Chair of the AAOMS Position Paper Task Force), are of the opinion that Fosamax causes osteonecrosis of the jaw. Dr. Marx's conclusions are well known to this Court and have been presented in numerous publications, including his text. On May 12, 2008, Dr. Ruggiero was deposed in the Novartis Aredia/Zometa MDL. Dr. Ruggiero testified, unequivocally, as follows:

Q: Do you view Fosamax as a causative agent for osteonecrosis of the jaw?

A: Yes.

Q: Am I correct in understanding that you view Fosamax as causing it as [sic] a lower incidence rate than the IV bisphosphonates?

A: Yes.

(Exh. 8.0007: 38:13-38:19) Additionally, in the same *JOMS* supplement in which the AAOMS Position Paper was published, the editor of the journal, Dr. Leon Assael (a paid Merck and Novartis consultant), published a review piece entitled: *Oral Bisphosphonates as a Cause of Bisphosphonate-*

Related Osteonecrosis of the Jaws: Clinical Findings, Assessment of Risks, and Preventive Strategies, J Oral Maxillofac Surg 67:35-43, 2009 Suppl 1 (Exh. 2.1009), which he began with the following sentence: "Oral bisphosphonates are known to have potentially profound effects on oral health. A review of the evidence supporting answers to key clinical questions is necessary to assist surgeons in the care of their patients who are receiving oral bisphosphonates." (*Id.* at 35.)

Dr. John Fantasia authored another article appearing in the same special supplement, dedicated to bisphosphonates, in which he presented the following conclusions:

> The overall risk of osteonecrosis in individuals taking the nBPs [nitrogen-containing bisphosphonates] has not been clearly defined; however, epidemiologic studies and clinical experience have indicated that an increased risk exists of bisphosphonate-related osteonecrosis of the jaws (BRONJ) developing in patients receiving intravenous nBPs and a lesser risk with oral nBP medications.

Bisphosphonates – What the Dentist Needs to Know: Practical Considerations, J Oral Maxillofac Surg 67:53-60, 2009 Suppl 1 (Exh. 2.1010). Other articles echoing the causal relationship also appeared in the same supplement: Arce, K, et al., *Imaging Findings in Bisphosphonate-Related Osteonecrosis of the Jaws*, J Oral Maxillofac Surg 67:75-84, 2009 Suppl 1 (Exh. 2.1011); Marx, RE, *Reconstruction of Defects Caused by Bisphosphonate-Induced Osteonecrosis of the Jaws* , J Oral Maxillofac Surg 67:107-119, 2009 Suppl 1 (Exh. 2.1012).

Defendant also fails to disclose to the Court the 2006 American Academy of Endodontists Special Committee on Bisphosphonate Position Statement, in which the AAE committee concluded:

> Therefore, until further information is available, it would appear prudent to consider all patients taking bisphosphonates to be at some risk for ONJ, with the recognition that the magnitude of the risk probably varies depending upon the particular bisphosphonate taken, patient factors (e.g., concurrent drugs, diseases, etc.), and dental treatment history. The information at this time suggests that patients taking I.V. bisphosphonates have a higher risk for developing ONJ, while patients taking oral bisphosphonates have a lower risk.

(AAE position stmt. p.2, Exh. 2.1013.)

Nor did Defendant disclose the American Academy of Oral Medicine Position Paper, published in December of 2005, which addressed theprevention of bisphosphonate-associated osteonecrosis (BON). The committee stated the results of the effort as follows:

> There is strong evidence that bisphosphonate therapy is the common link in patients with BON. The pathobiological mechanism leading to BON may have to do with the inhibition of bone remodeling and decreased intraosseous blood flow caused by bisphosphonates. People at risk include patients with multiple myeloma and patients with cancer metastatic to bone who are receiving intravenous bisphosphonates, as well as patients taking bisphosphonates for osteonecrosis.

(AAOM Position Paper in *JADA*, p. 1658, Exh. 2.0338.)

Referencing the 2006 American Dental Association Expert Panel bisphosphonate recommendations, Defendant neglects to mention the 2008 oral bisphosphonate-specific recommendations in which the Panel concluded: "All patients taking the drug should be informed that -oral bisphosphonate use places them at very low risk of developing BON of the jaws . . .-the low risk of developing BON maybe minimized but not eliminated. . . ." Edwards, BJ, et al.*Updated Recommendations for Managing the Care of Patients Receiving Oral Bisphosphonate Therapy: an Advisory Statement from the American Dental Association Council on Scientific Affairs* , JADA; 139(12):1674-1677 (2008) (Exh. 2.1014). In fact, the full July 2008 white paper of the ADA's expert panel recommendations undercuts every single argument made by Defendant in its *Daubert* challenge:

> Though it is early in the investigative stage, the relationship between bisphosphonate exposure and the occurrence of osteonecrosis of the jaw appears to be consistent with Bradford-Hill's criteria for causality: *strength of association*, i.e., individuals on bisphosphonate therapy appear to present a higher risk of BON than nonusers; *temporal association*, i.e., bisphosphonate exposure precedes the occurrence of BON; a *biological gradient*, with higher doses of bisphosphonaets resulting in more rapid

> and serious presentations of BON; *consistency*, i.e., the effect (BON) has been observed by several investigators; *specificity*, i.e., BON is seen in cancer and bone and mineral metabolism disease (osteoporosis and Paget's disease of the bone); and *biologic plausibility*, i.e., the event is defined by the mechanism of action of the drug.

(Exh. 4 to Dr. Hellstein deposition, for easy reference, attached hereto as Exh. 2.1015, p. 8.)

While Defendant mentions the *Canadian Consensus Practice Guidelines*, it fails to inform the Court that it was "on the in" in the drafting of those guidelines and, in fact the draft of the guidelines included the following statement: "Bisphosphonate treatment appears to be the most important risk factor for the development of ONJ." (Exh. 1.0660, p. 00126979.) Merck had the opportunity to influence the Canadian Guidelines drafting just as it did with the earlier version of the AAOMS position paper. (Exh. 1.0660, p. 00126975, Exh. 1.0113.)

D. A Review of Defendant's Experts' Causation Analyses Outside of Litigation Demonstrates the Validity of the Scientific Methodology Employed by the PSC's Experts.

Defendant's *Daubert* argument necessarily boils down to the issue of whether the experts' methodology constitutes "junk science". A review of Defendant's experts' scientific causation analyses in instances outside of litigation demonstrates that the PSC's experts did not rely on "junk science" to support their opinions that Fosamax causes ONJ.

For example, Dr. Glickman is of the opinion that a drug known as dapsone causes a condition known as methemoglobinemia, and published his findings in a case report, as follows: "'All patients on dapsone are predisposed to developing methemoglobinemia." (Exh. 4.0005: 94:3-103:24 & depo Exh. 4 to his depo.) To reach that opinion, Dr. Glickman relied upon the underlying mechanism of action, his clinical experience, but could identify no case-control studies in support of the conclusion. (Id..)

Dr. Eisenberg expresses the opinion that certain radiation therapy is known to cause osteonecrosis of the jaw. In support of her opinion, as a practicing oral pathologist, she relies on her clinical experience, case reports and case series, and biologic plausibility. (Exh. 4.0004: 16:6-17:17, 21:23-24:17. Dr. Eisenberg agrees that reasonable experts can approach the same causation issue and draw different conclusions applying the same methodology. (Exh. 4.0004: 143:17-145:14.) This is precisely why *Daubert* focuses on the approach, rather than the conclusions.

IV. THERE IS SOUND SCIENTIFIC EVIDENCE THAT FOSAMAX HAS VERY LIMITED FRACTURE REDUCTION EFFICACY.

In response to Defendant's motion to exclude the testimony of its former consultant, Dr. Gordon Guyatt, the PSC incorporates by reference its memorandum of authorities in support of the PSC's May 8, 2009 *Daubert* motion, relating to the limited fracture reduction efficacy of Fosamax.

Regarding the challenge of Merck to Dr. Guyatt's credentials, this Court need only review Dr. Guyatt's curriculum vitae. Dr. Guyatt has authored over 650 peer-reviewed in the area of evidence-based medicine. Dr. Guyatt also served as a consultant to Merck, performing and publishing meta-analyses of its clinical trials. Prior to this litigation, Dr. Guyatt has engaged in extensive meta-analysis of Fosamax's fracture reduction efficacy, at the request and sponsorship of Merck. (Exh. 5.0004: 68:24-75:2.)

While Merck refers to Dr. Guyatt and ONJ in the same sentence, the PSC has made it expressly clear that Dr. Guyatt is not offering any opinion testimony on the topic of ONJ. Dr. Guyatt's "areas of research include but are not limited to: measuring quality of life in patients with chronic disease; measuring the effectiveness of therapy in patients with chronic diseases; health technology assessment; systematic overview methodology; evidence-based health-care; and

guidelines development." (Exh. 6.0004: pp. 1-2.) The focus of his testimony is to explain the limited fracture reduction efficacy and corresponding issues. Most of these opinions have previously been presented, peer-reviewed, and published in the public domain in the following article, which he co-authored: Alonso-Coello P, Garcia-Franco AL, Guyatt G, Moynihan R. Drugs for pre-osteoporosis: prevention or disease-mongering? *BMJ* 2008; 336: 126-129, a copy of which is Attachment "B" to his report (attached hereto as Exh. 2.0103).

Dr. Guyatt explains that the diagnosis of "osteoporosis" is controversial, as the main criteria upon which the bone mineral density T-score evaluation is based is "'somewhat arbitrary'", according to the authors who created the T-score threshold; the -2.5 SD value were proposed for epidemiological study cut-offs, rather than for clinical practice. (Exh. 6.0004: p. 3.) Just as Dr. Santora explained that osteopenia is not a disease, (Exh. 3.0010: 332:7-15.) Dr. Guyatt testified that osteoporosis is not a disease. (Exh. 5.0004: 119:24-120:15.)

> A: So, in other words, one of the controversies that is implicit in the conversation we're just having, it is not - - the World Health Organization says this is osteoporosis. . . [I]t's not like tuberculosis; right? Tuberculosis we know is you get the tubercle bacillus and it does certain things to your body. Cancer we know; you can cut it up and look at it under the microscope. Osteoporosis, we are into a different ball game where there is – where there is a considerable amount of arbitrariness about what you call osteoporosis. So one of the controversies is what should be appropriately labeled as osteoporosis.

(Exh. 5.0004: 119:12-119:23.) Dr. Guyatt further illustrates, "When we say osteoporosis is a controversial condition, there's a number of things to which we refer that are emerging in this conversation, but it may be - - I would be - - is aging a disease; right? To me, no, it's not. And there are certain things that go along with aging, sad story as it is, that, you know, is it a disease that I now have to wear reading glasses, et cetera, et cetera." (Exh. 5.0004: 120:3-120:10.)

Dr. Guyatt, through his experience and training as a methodologist focused on risk-benefit analysis, is well qualified to opine on the clinical propriety of promoting Fosamax use for women without osteoporosis, since the condition "osteopenia" includes more than half of all white post-menopausal women in the United States. (Exh. 6.0004: p. 3.)

Consistent with the evidence presented in the PSC's *Daubert* motion pertaining to the limited fracture reduction efficacy data for Fosamax, Dr. Guyatt puts into the appropriate context the limitations on the fracture reduction data which Merck has and warns against inferring a similar benefit for a high risk group, such as severe osteoporotics with prior vertebral fracture, to a law risk group, such as osteopenics. (Exh. 6.0004: pp. 4-6.) Dr. Guyatt explains that the fracture reduction data that Merck has shows a limited duration of fracture reduction efficacy, and for a limited population of patients. (Exh. 6.0004: pp. 4-6.) Additionally, "[a]s with other attempts to define and treat new categories of pre-disease, such as pre-hypertension,and pre-diabetes, this move to treat pre-osteoporosis raises serious questions about the benefit-risk ratio for low risk individuals, and about the costs of medicalising [Canadian spelling] and potentially medicating an enormous group of healthy people." (Exh. 6.0004: p. 6.) Accordingly, Dr. Guyatt's review of the fracture reduction data lead him to the following conclusions:

> Clinical trial efficacy demonstrates a period of utility for women which diminishes after a certain duration. It is therefore not in patients' best interest to promote the use of Fosamax for the low-risk population and thereby exhaust the utility window for Fosamax use. That is, as women age most will increase their risk – the optimal utility for use of the drug will be in periods of higher risk.

(Exh. 6.0004: p. 5.)

Contrary to Defendant's assertion that Dr. Guyatt is attempting to express opinions relative to Merck's marketing, he is not; he simply places Merck's marketing efforts to non-osteoporotics

in the context of the data about which he opined:

> Since the mid-1990s, drug marketing in the United States and elsewhere has encouraged treatment of younger postmenopausal women at relatively low risk of fracture. Regarding alendronate sodium (Fosamax), I have reviewed internal documents relating to Merck's marketing of Fosamax and these are completely consistent with the inferences we made in our BMJ paper of 2008. [redacted] [14] While the propriety of this marketing efforts will be for others to discuss, it is important for purposes of this opinion to present the background relative to the topic of the utilization of bisphosphonates in the osteopenic population.

(Exh. 6.0004: p. 5; [redacted]

These opinions are entirely within Dr. Guyatt's scope of expertise as a medical physician and epidemiologist, focusing in on the evidence-based medicine approach to determining the true, as compared to putative, benefits conferred by a particular pharmaceutical agent - - in this case, Fosamax. This Court should deny Defendant's *Daubert* challenge to Dr. Guyatt's testimony.

V. THE PSC'S REGULATORY EXPERTS ARE COMPETENT TO OPINE ON MERCK'S OBLIGATIONS TO PATIENTS AND THEIR PHYSICIANS.

A. Dr. Suzanne Parisian Is Well Qualified to Render Opinions as to the Issues Before this Court.

Defendant mischaracterizes Dr. Parisian's experience and expertise as a regulatory expert and moves to exclude her entire testimony. As numerous courts have previously held, Dr. Parisian is qualified to offer expert testimony on FDA regulatory and labeling matters.

i. Dr. Parisian Has Extensive Knowledge, Training, and Experience in the Field of FDA Regulations and Drug Labeling.

Dr. Parisian has been proffered as a regulatory expert to opine on regulatory and labeling issues and is qualified to testify as an expert under Federal Rule of Evidence ("FRE") 702, which

sets forth the standard for admissibility of expert testimony as one may be qualified to testify as an expert "by knowledge, skill, experience, or training." Dr. Parisian is well qualified to testify in this matter by all four of the categories.

Dr. Parisian is a physician who is board certified in anatomic and clinical pathology with a masters degree in biology. She is a former FDA Medical Officer and currently is president of a regulatory and medical consulting firm specializing in FDA regulatory issues. (Exh. 6.0007: ¶1-2.) From 1991 to 1995, she served as a Commissioned Officer in the US Public Health Service achieving the rank of Lieutenant Commander. She was primarily assigned to the Center for Devices and Radiological Health ("CDRH") at the FDA. (*Id.* at ¶2.)

From 1991 to 1993, she served as a FDA Medical Officer in the Office of Health Affairs ("OAH"), a staff office within CDRH where she provided regulatory support to both the FDA's office of Compliance and Office of Device Evaluation. There, she was responsible for the preparation and review of health hazard and health risk assessment analyses, safety alerts, physician and layperson communications, adverse event reports ("AER"s) and medical literature, product labeling, promotional and advertising information, and corporate records. During this time she was responsible for 162 health risk assessments. In order to make these health risk assessments the FDA required review of labeling and adverse events under the Food, Drug, and Cosmetic Act. (*Id.* at ¶3.) From March 1993 to December 1993, she was a Medical Officer in the Office of Device Evaluation ("ODE"), Division of Reproductive, Abdominal, Ear, Nose, and Throat, and Radiology Devices at the FDA. (*Id.* at ¶5.) This Center had responsibility for bone densitometer technology. (Exh. 5.0007: 44:18-57:19.) As Chief Medical Officer assigned to that Center she was involved in the oversight of the bone densitometer algorithm used to assess women's fracture risk from osteoporosis. One of

her responsibilities in the Center was to address concerns raised by the FDA that these algorithms were not safe and effective. Dr. Parisian initiated meetings with different manufacturers of densitometers to discuss what they were (and were not) allowed to say about diagnosing bone fracture risk in terms of their marketing and development of the algorithm. (Exh. 5.0007: 56:3-58:18.)

In her capacity as Medical Officer, she developed a specialized expertise in federal regulatory procedures and compliance. She was called upon by the FDA to provide the agency's interpretation of food and drug laws as they pertain to medical products, as well as the roles of the manufacturer and the health care providers. She served as FDA's official agency representative at medical meetings and seminars where she was asked to monitor the promotional activities of manufacturers to ensure compliance. (Exh. 6.0007: ¶8.)

Because of her knowledge and expertise, Dr. Parisian was also frequently asked to train FDA reviewers in the design, methodology, and evaluation of clinical data in investigational and pre-market applications and to train other medical officers on the process for health risk assessment and health evaluation. (*Id.* at ¶6.) Notably, Dr. Parisian was requested by the agency to act as FDA's own expert witness in administrative hearings. (*Id.* at ¶3.) The fact that Dr. Parisian does not currently treat patients and is not a specialist in osteonecrosis of the jaw ("ONJ") in no way lessens her expertise or the admissibility of her opinions in this case, as Dr. Parisian is not testifying as a general causation expert. Indeed, Dr. Parisian's experience is on par with that of the defendant's regulatory experts, Drs. Rarick and Shames, who also do not treat patients. (Exh. 4.0007: 44:4, 45:5, 251:9-252:12; Exh. 4.0008: 45:10-46:19.) Also like Drs. Rarick and Shames, Dr. Parisian's training and experience, upon which her opinions are based, concern FDA regulations, procedures,

and labeling, and are not specific to any one drug or device.

Merck's motion to exclude Dr. Parisian's expert opinions ignores the FDA's reliance on her expertise. Moreover, Merck's own regulatory experts, Drs. Rarick and Shames offer no opinion that Dr. Parisian lacks the qualifications to serve as a regulatory expert in this case.

Since leaving the FDA, Dr. Parisian continues to consult on FDA issues. She provides information and expert opinions to individuals, manufacturers, and organizations regarding FDA requirements. (*Id.* at ¶12.) These topics include adverse event reports, labeling, and premarket and post-market applications for devices, biologics and drugs. (*Id.*) She is also an invited lecturer and consultant to pharmaceutical companies regarding FDA regulations addressing premarket clearance, design of clinical trials, product labeling, Corrective and Preventive Action ("CAPA"), and Good Manufacturing Practices ("GMP"). (*Id.*)

Defendant also argues that Dr. Parisian's opinions are not admissible, claiming her regulatory experience is limited only to medical devices. Defendant ignores the fact that during Dr. Parisian's tenure at the FDA she worked on numerous projects involving devices, biologics, *and* drugs. (*Id.* at ¶4.) Indeed, she has vast experience in the regulatory review process for all three types of regulated entities. For example, as the sole medical officer tasked specifically with drug safety concerns regarding ACE inhibitors, she reviewed both the drug and device adverse event reports and medical literature. (*Id.*) She performed a health risk assessment and ultimately made a clinical application, clinical trial, and labeling evaluation. (*Id.*)

Merck correctly asserts that Dr. Parisian was a medical officer in the Office of Health Affairs, a staff office within the Center for Medical Devices and Radiological Health ("CDRH"). While there, she supplied regulatory support and oversight to both the FDA's Office of Compliance and

the Office of Device Evaluation with responsibilities for FDA compliance as it pertains to both drugs and devices. (*Id.* at ¶15.) The regulatory procedures and compliance issues for medical devices and drugs are very similar and both are governed by the FDCA. 21 U.S.C. 301,*et seq*. Dr. Parisian has made clear that the analysis, methodology and the processes she used to perform her regulatory activities and to perform her risk assessment responsibilities are similar for both drugs and devices.

ii. Defendant Mischaracterizes the Case Law Regarding Dr. Parisian, and its Selected Cases Do Not Support its Position to Exclude Dr. Parisian's Testimony.

Defendant relies on three United States District Court opinions in which Parisian offered expert testimony. Defendant's reliance on these selected cases is misplaced. A careful review of the District Court cases cited by Defendant actually affirms the admissibility and reliability of Parisian's opinions.

The first offered opinion is *In re: Prempro Prods. Liab. Litig.*, 554 F Supp. 2d 871 (E.D. Ark. 2008). This case involved a claim for compensatory and punitive damages resulting from the plaintiff's use of the drug Prempro. The case was tried to a jury in two phases. During the compensatory first phase of the trial, Dr. Parisian was permitted to testify on regulatory matters and the court found that Dr. Parisian's testimony "has met the *Daubert* threshold." *Id.* at 879. The court further ordered that "Defendant's remaining criticism of Dr. Parisian's testimony and report can be addressed during cross-examination." *Id.* The court concluded that "Dr. Parisian can give her opinions on "the reasonableness of a pharmaceutical company's actions based on her observations over the years and her understanding of the regulations." *Id.* That case resulted in a verdict for the plaintiff who received an award of compensatory and punitive damages. In its *Daubert* motion before this Court, Defendant failed to mention to the court that the motion to strike her regulatory

opinions in that case was denied and the compensatory damage verdict was upheld.

The second case Defendant cites is *In re: Human Tissue Prods. Liab. Litig.*, 582 F. Supp. 2d 644 (D.N.J. 2008). There, Dr. Parisian was proffered as an expert to give testimony on medical causation issues. The testimony elicted from Dr. Parisian specifically focused on two issues of medical causation, 1) the transmission of HIV, HBV, HCV, syphilis, cancer, and prions, and 2) the incubation period for these diseases. The trial court limited her testimony on medical causation. Again, Defendant fails to mention, in the same case, that Dr. Parisian was also proferred to testify on regulatory issues and the court permitted her to do so under Rule 702. *Id.* at 684. In the present case, Dr. Parisian has made clear that she does not intend to give opinion testimony on the issue of medical causation in this matter.

Defendant also relies on *Oakberg v. Zimmer Inc.*, Case No. CV –03-47-BU- SHE, 2004 WL 5503779 (D. Mont. 2004). This is the sole isolated opinion in which a District Court has excluded Dr. Parisian's regulatory testimony. However, not mentioned by Defendant is the order issued approximately 11 weeks later by the Honorable Judge Tunheim of the United States District Court for the District of Minnesota. *See Lillebo v. Zimmer, Inc.*, 2005 WL 388598 at *6 (D. Minn. 2005). That case involved the same defendant, Zimmer Inc., the same Zimmer prosthetic device, the same plaintiff and defense attorneys, and the same federal regulatory expert, Dr. Parisian.

In direct contrast to the *Oakberg* decision, that court in *Lillebo* held that Dr. Parisian was "permitted to testify to the general nature of approval and regulatory process, the FDA's general expectations with respect to testing and marketing of new products, Zimmer's actions in that respect, and Parisian's opinions as to whether those actions were reasonable or appropriate." *Id.* at *5. The court held that such testimony was relevant to the plaintiff's allegations that Zimmer failed to

conduct adequate testing of their product. Further, the court held that Dr. Parisian's testimony was clearly relevant to the plaintiff's design claims. *See id.* The court specifically held that Dr. Parisian's opinions are reliable: "[Dr.] Parisian's opinions are based on her experience and were formed through application of the same methodology she used at the FDA." *Id.* at *6. The court observed, "Zimmer's objections regarding the reliability of Parisian's opinions relate almost entirely to the factual basis for her opinions. 'The factual basis of an expert opinion goes to the credibility of the testimony, not the admissibility.'" *Id.* (citing *Bonner v. ISP Tech., Inc.*, 259 F. 3d 924 at 930 (8th Cir. 2001)).

Several other United States District Courts have allowed Dr. Parisian to testify and have held her opinions to be qualified, relevant, and reliable. *See, e.g., Reece v Astrazeneca Pharmaceuticals, LP*, 500 F Supp. 2d 736 (S.D. Ohio, 2007) (holding Dr. Parisian's testimony admissible on "regulations governing the approval, labeling, advertising and marketing of pharmaceutical and medical products; the processes by which the FDA determines the efficacy and safety of new drugs and new drug applications; the issues the FDA considers in the development of product labeling and marketing information; and a manufacturer's responsibility within this system"); *In re Guidant Corp. Implantable Defibrillators Products Liability Litigation* , 2007 WL 1964337 (D. Minn. June 29, 2007) (holding that "Dr. Parisian is allowed to testify as to the general nature of the approval and regulatory process including compliance with FDA regulations and guidelines, the FDA's general expectations with respect to testing and marketing of new products, Guidant's actions in that respect, and her opinion as to whether Guidant's actions were reasonable and appropriate"); *Linsley v. C.R. Bard, Inc. et al.,* 2000 WL 343358 (E.D. La. March 30, 2000) (holding that Dr. Parisian's expert testimony was admissible regarding the acceptability of the surgical mesh label under FDA

standards).

To summarize, the courts that have heard *Daubert* challenges to Dr. Parisian's testimony have almost universally ruled that she is permitted to testify to the following issues: 1) the complex regulatory framework governing the approval, labeling, advertising, and marketing of pharmaceutical and medical products, 2) the FDA's process for determining efficacy and safety of pharmaceutical drugs, including safety testing, monitoring, and reporting, 3) FDA requirements for the development of product labeling and marketing, and 4) manufacturer responsibility and compliance with FDA regulations and guidelines. These include, but are not limited to IND and NDA drug submissions, adverse event reporting, labeling requirements and pharmacovigilance/post-marketing surveillance.

iii. Dr. Parisian's Testimony Concerning the Requirements of the Federal Regulations Regarding Drug Development, Labeling, Approval, Pharmacovigilence, and the Reasonableness of a Pharmaceutical Company's Actions Is Necessary to Educate the Lay Jury on These Complex Matters.

The PSC offers Dr. Parisian's expert testimony with respect to four issues: (1) The role of the FDA and the duty and obligations of prescription drug manufacturers; (2) FDA's approval of Merck's oral Alendronate (Fosamax) NDA# 20-560 for prevention and treatment of post-menopausal osteoporosis in women at increased risk; (3) Merck's interactions with FDA regarding reporting and investigation of osteonecrosis of the jaw; and (4) Merck's communications of osteonecrosis of the jaw risks to healthcare professionals and patients.

These intricate issues require the specialized knowledge and expertise of an FDA regulatory expert such as Dr. Parisian who will assist the jury with understanding these regulations, requirements, and procedures. Her opinions offered in this matter are highly relevant and will assist the trier of the fact in determining the duties and obligations of a drug manufacturer with regard to

its drug and the plaintiff. *See* Fed. R. Evid. 702.

Defendant characterizes Dr. Parisian's testimony as being merely her own personal views under the guise of a narrative history, and that she bases her opinions on an incomplete review of company documents. At page 47, Defendant alleges that Dr. Parisian failed to review the NDA and internal company documents in their entirety, and based her opinions on a limited review of a few documents scattered across the period between 1981 and 2005. Defendant's approach would require Dr. Parisan to literally review nearly 1 million pages of documents produced in this litigation. If the Court were to adopt such an onerous standard it would have the effect of barring not only Dr. Parisian, but also Defendant's regulatory experts, Drs. Shames and Rarick who reviewed selected portions of the NDA and internal company documents. (Exh. 4.0008: 88:10-88:21; Exh. 7.0001: pp. 1,5, Exh. "C"). As Defendant is well aware, Dr. Parisian reviewed the index of Defendant's entire NDA production in this matter. (Exh. 6.0008: ¶ 2; Exh. 6.0007: pp. 143-145.) She selected those documents which, from their objective coding, appeared to be the most pertinent to the issues involved in this litigation, identified them on a spreadsheet, and requested that counsel download the documents and send them to her on disc. (Exh. 6.0008: ¶ 2.) She then received and reviewed the selected documents, and copies of the discs were sent to Merck's counsel well prior to her deposition. (Exh. 6.0008: ¶ ¶ 2-3; Exh. 5.0007: 5:14-6:10, 37:4-37:10, 66:18-70:15.) The spreadsheet of the documents thus selected and reviewed by Dr. Parisian is Attachment "A" to her declaration. (Exh. 8.0008: ¶ 4, Attachment "A".) As Dr. Parisian indicates: "The total number of NDA documents selected and reviewed by me exceed 1,500 and the total number of pages was in the tens of thousands." (Exh. 8.0008: ¶ 2.) Compare the spreadsheet to Dr. Rarick's Appendix "C" to her report and one can easily see that the documents selected and reviewed by Dr. Parisian easily

match and likely exceed the number reviewed by Dr. Rarick. Notably, Dr. Rarick testified that the NDA alone for Fosamax is hundreds of thousands of pages and that no single medical officer or reviewer reviews the entire IND or NDA. (Rarick depo.) Defendant's attacks on the facts underlying an expert's opinion go to the weight, not the credibility, of the testimony. *Bonner,* 259 F. 3d at 930.

Dr. Parisian's testimony and use of internal company documents will help to educate and inform the jury. Her analysis of the documents is consistent with the method she employed at the FDA to determine and assess regulatory compliance and her testimony evaluating these materials is similar to that of Dr. Levy in *In re Welding Fume Product Liability Litigation*, 2005 WL 1868046 at *17 (N.D. Ohio August 8, 2005), where the Court held:

> First, it is worth noting that "an expert on the stand may give a dissertation or exposition of scientific or other principles relevant to the case, leaving the trier of fact to apply them to the facts." Fed. R. Evid. 702 (Advisory Committee Notes to 1972 Proposed Rule). Thus, a "narrative" by an expert is not automatically inadmissible; it is only when, as in *In re Rezulin*, the narrative is purely "a repetition of the factual allegations in plaintiffs' complaint," involving "nothing technical or scientific," that a court might find the expert testimony unhelpful, because the expert is providing only "simple inferences drawn from uncomplicated facts." *In re Rezulin*, 309 F. Supp. 2d at 551 and n. 67. In this case, the great majority of the documents and articles that Dr. Levy is reviewing and comparing are complicated, and the inferences those documents may or may not support are not at all simple. It is through the application of his expertise that Dr. Levy may allow the trier of fact to better understand what the documents do (and don't) mean, and, thus, what the defendants did (or didn't) know. It is not the case that "the untrained layman [is] qualified to determine intelligently and to the best possible degree the[se] particular issue[s] without enlightenment" from experts. Fed. R. Evid. 702 (Advisory Committee Notes to 1972 Proposed Rule).

Likewise, Dr. Parisian must review internal company and FDA documents that raise complex inferences involving regulatory issues that are best explained by the application of her specialized experience, training skill, education, and knowledge. By applying this expertise she is able to assist

the jury in interpreting the meaning of the documents and Merck's conduct.

iv. Dr. Parisian Does Not Offer Testimony in this Matter as to Ethics, Nor to Merck's Motive or Intent.

Dr. Parisian will offer testimony regarding 1) the standard of care of a pharmaceutical company in the position of Merck with respect to the study, approval, and post-market surveillance of Fosamax, and 2) Merck's breach of that standard of care as reflected in numerous documents upon which she bases her opinions. However, Defendant distorts this testimony, claiming it is a judgment regarding the knowledge, motives, and intent of Merck and its employees. In reality, her testimony draws no such conclusions. Dr. Parisian merely explains what knowledge was *available* for Merck and its employees to know, what information it *should* have known as a manufacturer of prescription drugs in order to meet the standard of care, and what the company *should* have done upon learning such information under the regulatory scheme. Like any expert, Dr. Parisian's role is to inform the jury about the complex matter of FDA regulations and labeling. [14] This role includes telling them what a prudent pharmaceutical company would do, and the ways in which Merck's actions meet or fall short of the actions of a prudent company.

As has been held by numerous courts, Dr. Parisian is qualified to testify as to FDA regulations, labeling, premarket approval, and postmarket surveillance, including the actions of a pharmaceutical company and whether it met the applicable standard of care. Accordingly, this Court should deny Merck's motion to exclude the testimony of Dr. Suzanne Parisian.

B. Dr. Curt Furberg Is Well Qualified to Render Opinions as to the Issues Before

[14] A review of her expert report, when compared to those of Dr. Shames and Dr. Rarick, demonstrates that her discussion of the role and limitations of the FDA, as well as of the pharmacovigilance duties of the manufacturer, are coordinates directly with those observed by the majority in the United States Supreme Court opinion in *Wyeth v. Levine*, 129 S.Ct. 1187, - - U.S. - - (March 4, 2009). Notably, the reliability of Dr. Parisian's opinions relating to the federal regulatory process and limitations is evidenced by the fact that her report in this case was prepared well prior to the rendering of the opinion in *Levine*.

this Court.

Dr. Curt Furberg is an expert in: (1) Drug Safety; (2) Clinical Trials – including, their design, conduct, interpretation, communication, reporting, follow-up and the medical and scientific standard of care associated with each aspect; (3) Public Health – issues as they relate to the use of drugs to treat disease, including their proper indication; and (4) Risk-benefit analysis. Dr. Furberg's vast knowledge from decades of experience and demonstrated skill makes him eminently qualified to offer his expert opinion testimony in these fields. Under Rule 702 one may be qualified to testify as an expert, "by knowledge, skill, experience, or training." As demonstrated below, Dr. Furberg is qualified to testify under all four of the categories.

Dr. Furberg will testify about whether Defendant's conduct comported with industry standards and regulatory guidelines. This is the proper subject of expert testimony in a pharmaceutical drug products liability case. In In re Diet Drugs Products Liab. Lit., 2000 WL 876900, *11 (E.D. Pa. 2000), the court stated that expert witnesses may testify for the identical purposes as Dr. Furberg:

> [Plaintiffs' experts] are fully qualified to opine on the medical facts and science regarding the risks and benefits of the diet drugs in question and to compare that knowledge with what was provided in the text of labeling and warnings on the diet drugs in question. In other words, [plaintiffs' experts] are qualified to render an opinion as to the labels' completeness, accuracy, and—it follows from that—the extent to which any inaccuracies or omissions could either deprive a reader or mislead a reader of what the risks and benefits of the diet drugs in issue are or were at the time the labeling was published.

i. Dr. Furberg Has Extensive Knowledge, Skill, Training, and Experience in the Fields of Drug Safety, Clinical Trials and Public Health.

Dr. Furberg was an investigator in the Fracture Intervention Trial (FIT)[15]. (Exh. 6.0002 ¶ 5a.) His experience in the field of drug safety is second to none. He has served on the Data Safety Monitoring Board of over 50 clinical trials. (Exh. 6.0002 ¶ 5b.) Pharmaceutical companies, State governments and the Federal government have sponsored these trials and programs. (Exh. 6.0002 ¶¶ 5, 6, and 10.) Some of the sponsoring pharmaceutical companies that worked with Dr. Furberg include: Sandoz, Wyeth, Bristol Myers, Pfizer (and of course as stated above defendant Merck). (Exh. 6.0002: ¶¶ 5 to 11.) Government entities that he has worked with include: the National Institute of Health (NIH), the National Heart Lung and Blood Institute (NHLBI), and the States of North Carolina and Oregon. (*Id.*) He has testified twice before Congress [16] on drug safety and submitted an amicus brief to the Supreme Court in *Wyeth v. Levine*.[17] Dr. Furberg has served as an expert witness for both Plaintiffs and Defendants on drug safety issues. (Exh. 6.0002 ¶ 5d.)

ii. Dr. Furberg's Testimony Concerning the Duty of Care and the Reasonableness of a Pharmaceutical Company's Actions Is Necessary to Educate the Jury on this Complex Issue.

Dr. Furberg's opinions are clearly stated in Section C, ¶ 20 of his report. These opinions include: (1) a recitation of the duty of care; (2) Merck did not actively pursue emerging safety signals based on Fosamax usage through research or analysis of available databases; (3) Merck denied that

[15] Merck selected Wake Forrest University as one of the centers for the FIT trial and a PhD, Sara Quandt, to run the trial. Dr. Furberg was the Principal Investigator and medical doctor selected to oversee the FIT Trial at Wake Forest University where he is a Professor of Public Health Sciences. As the Principal Investigator he supervised and was consulted by Dr. Quandt with the daily responsibility for running the trial.

[16] Once providing written testimony to the Senate Committee on Health, Education, Labor and Pensions. The second time testifying live in front of the House Committee on Energy and Commerce, Subcommittee on Oversight and Investigations and providing testimony regarding pharmaceutical companies oversight of drug safety, including applicable laws, regulations ***and the consequences of violations thereof***. Furberg report paragraph 8. (emphasis added).

[17] No. 06-1249, Brief of Amici Curaie Anju Budhwani, M.D.; Curt D. Furberg, M.D., Ph.D.; et al. in Support of Responent. Amici identified themselves as, "... health care providers, educators and public health advocates. Their professional responsibilities require that they balance the risks of various pharmaceuticals against their therapeutic benefit.... Amici have a professional interest in ensuring that the public health is protected through laws and public policies". Amiucs brief page 1.

evidence exists that Fosamax caused Osteonecrosis of the Jaw (ONJ) and engaged in efforts to downplay the role of Fosamax induced ONJ; (4) Merck ignored advice by experts in the relevant scientific community and has refused to broadly inform physicians and patients regarding the risk of Fosamax-induced ONJ, (5) Merck aggressively promoted and continues to promote Fosamax, even for off-label use; (6) the limitations of clinical trials related to detecting adverse events. (Exh. 6.0002: p. 8 and ¶¶ 50-57).

The Plaintiffs will introduce evidence concerning the safety data known to Merck, how that data was submitted to the FDA, and how that information was presented in the Fosamax label. Dr. Furberg will offer expert testimony, based on the facts in evidence and on his professional expertise, as to whether Defendant acted in accordance with industry and regulatory standards and, if not, the implications of Defendant's failures. He will also give his expert opinions on whether particular statements or representations made by defendants to the FDA and in the label were accurate based on the available information from the clinical trials. This testimony is not within the common knowledge of the jury, and therefore expert testimony is appropriate. *In re Diet Drugs Products Liab. Lit.*, 2000 WL 876900, *11.

These opinions do not constitute "personal opinions". An expert may testify concerning factual evidence and whether those facts meet industry standards. Whether a drug label comports with industry standards and FDA guidelines and regulations is not within the ordinary experience of jurors, and expert testimony concerning these matters is appropriate. Dr. Furberg may state, based on the evidence, whether defendants violated the standards of good practice in the pharmaceutical industry, both in regard to its interactions with the FDA and the Fosamax labels it published. *See, Lippe v. Bairnco Corp.*, 2002 WL 15630, at *2 (S.D.N.Y. 2002) (Chin, J.) ("An expert may properly

testify as to the customs and standards of an industry, and opine as to how a party's conduct measured up against such standards")(cits. omit.); *DePaepe v. General Motors Corp.*, 141 F.3d 715, 720 (7th Cir. 1998)(stating that an expert could testify that defendant's action saved money or that defendant's explanation for a decision is not sound). Few people in the world are more qualified than Dr. Furberg to give opinions on these topics.

Moreover, the duty of care in a clinical trial and the marketing of a pharmaceutical drug is a unique and complex duty. By definition, a clinical trial is testing the unknown effect of a new and potentially dangerous foreign substance on the human body. It is an experiment, conducted on humans, in which the risks and benefits to the patient are still unknown and the investigators are attempting to quantify. Since it is an experiment, that is putting human lives at risk, it requires an intense, careful and prudent evaluation of events and data and the accurate reporting thereof. Whether a company performed analysis correctly and in accordance with the standards of the medical community is absolutely the proper subject of expert testimony. *See, In Re Diet Drugs*, 2000 WL 876900, *11.

In articulating what the response of a prudent and responsible company should be to data gleaned from a clinical trial a careful balancing of known, unknown, suspected, probable and even unlikely outcomes must be considered. In the field of clinical trials, "ethics" possesses a highly specific meaning encompassing this concept. Dr. Furberg is offering expert testimony regarding the level of expected care within the field of clinical trials, not an abstract moral evaluation. Such ethical standards are the admissible subject of expert testimony precisely because they help illustrate the reasonable medical standard of care. *See, Andrade Garcia v. Columbia Medical Center of Sherman*, 996 F. Supp. 617, 627 (E.D. Tex. 1998) ("While it is true that there is no cause of action

for the breach of an ethical standard of care, testimony regarding ethical duties may be useful in informing the jury about the accepted standards of medical care which a reasonable health care provider would follow and in helping the jury to determine whether Defendants deviated from those standards.")(emphasis added); *see also*, *In re Guidant Corp. Implantable Defibrillators Products Liability Litigation*, 2007 WL 1964337 (D. Minn. 2007) (holding that an expert, "is allowed to testify as to the general nature of the approval and regulatory process including compliance with FDA regulations and guidelines, the FDA's general expectations with respect to testing and marketing of new products, Guidant's actions in that respect, and her opinion as to whether Guidant's actions were reasonable and appropriate"). This is the calculus Dr. Furberg performs everyday in his career as a professor, member of Data Safety Monitoring Boards, clinical investigator for pharmaceutical companies and advisor to the FDA.

iii. Defendant's Attempt to Limit Dr Furberg's Expertise by Defining the Negative Does Not Change the Fact That Dr. Furberg Is One of the Nation's Premier Experts in Clinical Trials, Drug Safety and Public Health.

Defendant seeks to make something of the fact that when Dr. Furberg discusses Merck's actions he is not an ONJ expert in but that observation is completely irrelevant to the correct analysis.[18] The number and type of drugs Dr. Furberg has consulted on in his career is long and distinguished. He has worked to help get safe and efficacious medications on the market and to get unsafe medications recalled. He has worked on blood pressure medications, Cox II pain medications, diabetic TZD medications, the "fen-phen" diet drug combination, Hormone

[18] For instance, the PSC has presented finite *Daubert* challenges to Merck's two regulatory experts on the ground that they are not qualified to testify on general causation. However, the challenge is limited solely to the experts' general causation opinions, and to their regulatory opinions (even though their regulatory opinions are inconsistent with the Supreme Court's holding in *Wyeth v. Levine*).

Replacement Therapy (HRT), and the Ginko Biloba natural herb supplement among others. Just like an architect can design an office building, an apartment, a library or a courthouse, by applying his knowledge, skill, experience, and training, Dr. Furberg can design, evaluate and interpret clinical trials on really any type of medication and has done so for decades.

Similarly, Merck's attempts to define Dr. Furberg as "not a labeling expert", "not an expert in evaluating animal studies", "not an expert in Regulatory Affairs", is merit less. These are really semantics which are nothing more than an attempt to hide from the fact that Dr. Furberg is an expert in Clinical Trials, Drug Safety and Public Health.[19] To say, Dr. Furberg is not an expert in, "Drug Labeling" is the equivalent to saying, "the surgeon is not an expert in cardiology". True the surgeon may not be a cardiologist, but the surgeon remains an expert in surgery and could perform surgery on your heart, without knowing the natural history of the disease that made the operation necessary. Dr. Furberg remains an expert in Drug Safety, Clinical Trials and Public Health. Dr. Furberg can interpret the data gathered by a pharmaceutical company and compare the data to the information put in the label or otherwise disclosed by the company. He can then opine if the valid scientific conclusions of the clinical trial are clearly and accurately articulated in the label. Accurately communicating the adverse event data is ultimately the responsibility of the pharmaceutical company. Dr. Furberg can therefore review and opine on the vast majority of the contents of any drug label, particularly those sections recounting the Clinical Trails, Adverse Events, Warnings and Precautions, based upon the public safety duty owed by the company.

For example, Defendant complains that Dr. Furberg in not an expert in animal studies and

[19] Interestingly, Dr. Shames admitted, under oath, that he was not a labeling expert. (Exh. 4.0008: 213:14-213:20.) At the conclusion of the deposition, after he conferred with Defendant's counsel, and upon questioning by Defendant's counsel, Dr. Shames recanted that testimony. (Exh. 4.0008: 251:2-252:2.)

reference the court to page 120-123 of his deposition. In that discussion, Defendant inquire if Dr. Furberg looked at the animal studies. Dr. Furberg's opinions that reference an animal study do not attempt to make complex assertions about the presence of "alendronate" or any complex scientific concept. His opinion speaks to the *conclusions* of the rat study. Stated on page 14, Section P, paragraph 33 of his report, Dr. Furberg's opinion regarding animal studies is: "A study in rats was reported in 1981 that bisphosponates can induce ONJ like lesions over 18 weeks. ... This publication raised potential safety concerns. ... Merck made no effort to replicate this finding ... and never disclosed to the FDA exactly what its consultant's opinions were...."

After his 30+ years of clinical trial experience Dr. Furberg is absolutely qualified to say that if a human clinical investigator sees a certain conclusion in a pre-clinical rat study, then that same investigator can and should use that rat study information to guide his design of the human trial. Is it really Merck's position that if a investigator designing a human clinical trial saw evidence of enlarged hearts, liver failure, or decreased bone density, etc in a rat study, that the same investigator should not consider that evidence in designing the human trial? Dr. Furberg, as an expert in designing, administering, evaluating and reporting human clinical trials, can absolutely opine how a competent investigator and responsible pharmaceutical company should use the data from an animal study to inform their human trials. The same logic holds true for each and every arbitrarily defined subject area in which the defense has questioned Dr. Furberg's qualifications.

iv. Dr. Furberg's Opinion on Limitations of Clinical Trials Related to Detecting Adverse Events Is Not Challenged.

In Dr. Furberg's declaration, page 8, ¶ "C" references that Dr. Furberg will also proffer an opinion on, "[t]he limitations of clinical trials related to detecting adverse events" and that his opinions on this topic are discussed in ¶ 50-57 of his report. Defendant's motion does not seem

to call into question Dr. Furberg's expertise in this area. To the extent Merck's motion does challenge these opinions the arguments rebutting such challenges are identical.

Dr. Furberg is one of the most qualified Drug Safety, Clinical Trials and Public Heath experts in the country. Major government agencies, legislative bodies, and pharmaceutical companies have sought his opinion, on exactly the types of matters at issue in the case. As such, this Honorable Court should deny Merck's motion to exclude the testimony of Dr. Furberg.

VI. CONCLUSION.

Defendant attempts to heighten plaintiffs' burden and mislead this Court by distorting the definition of "scientific method" and misapplying it to *Daubert*. Defendant would have the Court (and indeed, their own experts) believe that under *Daubert*, the "scientific method" requires 95% statistical certainty of a causal relationship as determined by an epidemiological study. Without it, Defendant asserts, plaintiffs' experts are precluded from relying on Bradford Hill and similar criteria that assess the totality of evidence do not apply in assessing causation. The defendants wrongly insist that *each* line of evidence on its own must meet the 95% statistical certainty test. The real world of clinical medicine does not operate this way, and neither does *Daubert*. Moreover, plaintiffs are not aware of a single court in the Second Circuit that has considered, much less required, these stratospheric standards in its *Daubert* analysis.

To the contrary, when all of the evidence is considered – i.e., the well-known basic pharmacology of Fosamax, its similarity in side effects to other bisphosphonates, the published case reports and case series of ONJ, the animal studies, the clinical studies in humans, the analysis of adverse reaction reports by FDA, and other epidemiological data, and the consensus found in textbooks and other learned sources – it is clear that the evidence is sufficient to

establish causation, and the methodology employed by the experts is reliable.

Accordingly, this Court should deny Defendant's Motion to Exclude Expert Testimony on *Daubert* Grounds.

* * *

RESPECTFULLY SUBMITTED, this 8th day of June, 2009.

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